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**UNIVERSITY OF
PLYMOUTH**

Left Atrial Posterior Wall Isolation in the Treatment of Atrial Fibrillation

by

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A thesis submitted to the University of Plymouth in partial
fulfillment for the degree of

DOCTOR OF MEDICINE

School of Medicine and Dentistry

August 2020

Acknowledgements

I am grateful to my friends and colleagues in the cardiology department at Derriford Hospital Plymouth who supported and assisted me by allowing me the time to conduct the studies as well as valuable advice on the research. I am also indebted to my current colleagues at Musgrove Park who have been understanding, encouraging and accommodating in allowing me to finish writing the thesis since I took up my post.

Specific thanks must go to Guy Haywood who has been an inspiration and great help throughout my career in cardiology. Guy's ideas, support and input into the design and planning of this MD have been invaluable.

I'm thankful to Dimitrios Panagopoulos who worked alongside me collecting data for the hybrid ablation series and was a valuable contributor to various abstracts and presentations. I'm especially grateful to Dimitrios, Ed Davies and Sid Kanoun for the many hours they spent measuring P waves on ECG's for me in their spare time.

David Tomlinson helped identify cases for the P wave study and offered manuscript advice. As did Malcolm Dalrymple-Hay who contributed extensively to the description of surgical AF ablation.

Ian Lines and Dan Newcomb both helped with the technical aspects of oesophageal pacing and integration with the EP mapping system. Similarly, Ian Rankin of Dot Medical lent a temporary pacing box for the oesophageal studies and was the key collaborator for the electroporation studies.

Lastly, but greatest of all, I must thank my wonderful wife Reema who has supported me during three years of research; putting up with moving jobs, house and the birth of our daughter Anokhi while I have often been absent. Without her understanding and support none of this would have been possible.

AUTHOR'S DECLARATION

At no time during the registration for the degree of *Doctor of Medicine* has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

Word count of main body of thesis: 44,352 (including references)

Signed



Date

28.8.20

Publications related to this MD thesis:

Furniss G, Panagopoulos D, Newcombe D, Lines I, Dalrymple-Hay M, Haywood G. The use of an esophageal catheter to check the results of left atrial posterior wall isolation in the treatment of atrial fibrillation. *Pacing Clin Electrophysiol*. 2018;1–11. <https://doi.org/10.1111/pace.13471>

Furniss G, Panagopoulos D, Kanoun S, Davies EJ, Tomlinson DR, Haywood GA. The Effect of Atrial Fibrillation Ablation Techniques on P Wave Duration and P Wave Dispersion. *Heart Lung Circ*. 2018 Feb 14. pii: S1443-9506(18)30065-9. doi: 10.1016/j.hlc.2018.02.003.

Min-Young Kim MRCP, Markus B Sikkell PhD, Ross J Hunter PhD, Guy A Haywood MD, David R Tomlinson MD, Muzahir H Tayebjee MD, Rheeda Ali PhD, Chris D Cantwell PhD, Hanney Gonna MRCP, Belinda Sandler MRCP, Elaine Lim, **Guy Furniss MRCP**, Dimitrios Panagopoulos MRCP, Gordon Begg MRCP, Gurpreet Dhillon MRCP, Nicola J Hill, James O'Neill MRCP, Darrel P Francis MD, Phang Boon Lim PhD, Nicholas S Peters MD, Nick W F Linton PhD, Prapa Kanagaratnam PhD. **A Novel Approach to Mapping the Atrial Ganglionated Plexus Network by Generating A Distribution Probability Atlas. *J Cardiovasc Electrophysiol*. 2018 Aug 31. doi: 10.1111/jce.13723.**

Publications during the research period unrelated to this MD

Vinit Sawhney, Giulia Domenichini, James Gamble, **Guy Furniss**, Dimitrios Panagopoulos, Pier Lambiase, Kim Rajappan, Anthony Chow, Martin Lowe, Simon Sporton, Mark J Earley, Mehul Dhinoja, Niall Campbell, Ross J Hunter, Guy Haywood, Tim R Betts, Richard J Schilling; **Thrombo-embolic events in left ventricular endocardial pacing: long-term outcomes from a multicentre UK registry, *EP Europace*, , euy107, <https://doi.org/10.1093/europace/euy107>**

Furniss G, Jimenez A, Harding SA. Balloon anchoring to place a Left Ventricular lead without the use of a CS guide. *EUROPACE*. 2015 Dec;17(12):1776. doi: 10.1093/europace/euv257. Epub 2015 Oct 7. PMID: 26445818

Furniss G, Liang M, Jimenez A, Harding SA. Wire externalisation for left ventricular lead placement in cardiac resynchronisation therapy: A step-by-step guide. Heart, Lung & Circulation. 2015 Nov;24(11):1094-103. doi: 10.1016/j.hlc.2015.04.173. Epub 2015 Jun 10

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Hybrid Ablation for Long-Standing Persistent AF. A 2 Stage Nonconcomitant Approach using the Cobra Fusion Device and Catheter Ablation - Single-centre Experience. J Villquarin, GO Furniss, D Panagopoulos, M Dalrymple-Haye, GA Haywood. STS Latin America 2017

Electrical isolation by electroporation of right ventricular myocardium in an ex-vivo beating porcine heart: a potential novel use of the alert internal cardioversion catheter GO. Furniss, I. Rankin, GA. Haywood. Europace (2017) 19 (suppl_3):iii246

DOI: <https://doi.org/10.1093/ehjci/eux152.007> Published:20 June 2017

Left Atrial Posterior Wall Isolation (The “Box Lesion Pattern”) in the treatment of Atrial Fibrillation: A single centre experience. **Europace**. (2016) 18 (suppl_2): ii13-ii17. DOI: <https://doi.org/10.1093/europace/euw272>

Non-concomitant Hybrid ablation for longstanding persistent atrial fibrillation: an initial single centre experience. GO Furniss, J Villquarin, D Newcombe, I lines, M Dalrymple-Haye, GA Haywood. Heart (2016) <http://dx.doi.org/10.1136/heartjnl-2016-309890.64>

Presentations at conferences:

Oral Presentations

G Furniss, I Rankin, G A Haywood. Electrical isolation by electroporation of right ventricular myocardium in an ex-vivo beating porcine heart: a potential novel use of the alert internal cardioversion catheter - Rapid fire abstract session 20th June 2017 – **EHRA-Europace, Vienna, Austria 2017**

G.Furniss, D Panagopoulos, DR Tomlinson, M Dalrymple-Hay, GA Haywood. Left Atrial Posterior Wall Isolation (The “Box Lesion Pattern”) in the treatment of Atrial Fibrillation: A single centre experience. **Heart Rhythm UK 2016**

Poster Presentations

Left Atrial Posterior Wall Isolation (The “Box Lesion Pattern”) in the treatment of Atrial Fibrillation: A single centre experience. G Furniss, D Panagopoulos, D Tomlinson, M Dalrymple-Hay, GA Haywood. **Asia Pacific HRS 2016**

The Effect of Different Atrial Fibrillation ablation strategies on surface ECG P wave duration. G Furniss, D Panagopoulos, EJ Davies, GA Haywood. **Asia Pacific HRS 2016**

Non-concomitant Hybrid ablation for longstanding persistent atrial fibrillation: an initial single centre experience. D Panagopolous, **GO Furniss**, J Villquarin, D Newcombe, I lines, M Dalrymple-Haye, GA Haywood. **CARDIOSTIM 2016, Nice**

Non-concomitant Hybrid ablation for longstanding persistent atrial fibrillation: Promising medium term results. **GO Furniss**, D Panagopoulos, J Villquarin, D Newcombe, I lines, M Dalrymple-Haye, GA Haywood. **BCS 2016, Manchester**

Non-concomitant Hybrid ablation for longstanding persistent atrial fibrillation: an initial single centre experience. **GO Furniss**, J Villquarin, D Newcombe, I lines, M Dalrymple-Haye, GA Haywood. **Heart Rhythm UK 2015, Birmingham 6th October 2015**

Abstract

The optimal approach for the ablation of persistent atrial fibrillation is undefined. Left atrial posterior wall isolation (LAPWI) is a promising lesion set, based on techniques for surgical AF ablation. The left atrial posterior wall can be isolated via catheter, surgical or hybrid ablation techniques. This MD thesis aims to inform a comparative trial of catheter versus hybrid ablation.

In series of catheter and hybrid ablation with left atrial posterior wall isolation in patients with atrial fibrillation outcomes are suggested to be superior to published outcomes of alternative lesion sets. A complete lesion set with intact LAPWI ablation lines is important for outcomes and one advantage of a two-stage hybrid ablation may be that it provides greater chance of electrical isolation. It also gives rise to significant reductions in surface ECG P wave duration and dispersion which are associated with better ablation outcomes, possibly due to autonomic modulation. The benefits of hybrid ablation come at a cost of complications, however. Newer catheter ablation technologies such as electroporation may reduce risks and experiments on porcine models described in this thesis demonstrate how this is possible and provide a future avenue for research and development.

A technique is also described for checking the LAPWI lesion set via the use of an oesophageal pacing electrode. Feasibility is demonstrated when compared to simultaneous intracardiac study and a standalone “outpatient” technique is developed. This technique could be used for research or as part of standard follow-up of LAPWI via catheter or surgery.

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List of Abbreviations

3D three-dimensional

AF atrial fibrillation

CTI Cavo-Tricuspid Isthmus

CFAE Complex Fractionated Atrial Electrograms

EPS electrophysiology study

GP Ganglionic Plexi

LA left atrium

LAA left atrial appendage

LAPW left atrial posterior wall

LAPWI left atrial posterior wall isolation

LIPV Left Inferior Pulmonary Vein

LsPsAF Longstanding persistent atrial fibrillation

LSPV Left superior Pulmonary Vein

LV left ventricle

ms millisecond

OP Oesophageal pacing

PAF Paroxysmal Atrial Fibrillation

PsAF Persistent Atrial Fibrillation

PV pulmonary vein

PVI pulmonary vein isolation

PW posterior wall

RA right atrium

RF radiofrequency

RIPV Right Inferior Pulmonary Vein

RSPV Right Superior Pulmonary Vein

RV right ventricle

VATS Video assisted Thoroscopic Surgery

For
Reema & Anokhi

Left Atrial Posterior Wall Ablation in the Treatment of Atrial Fibrillation

1 Chapter 1 - Introduction

1.1 Introduction

Atrial Fibrillation is the most common supraventricular arrhythmia, characterised by disorganised chaotic contraction of the atria. Although not life-threatening, the condition has a significant impact on quality of life and the thromboembolic risk is associated with substantial mortality and morbidity. In the Framingham Heart study the presence of AF was associated with a 50-90% increase in mortality¹. As the general population ages the prevalence of AF is increasing and with this the burden and cost on health services are rising.

1.1.1 History of Atrial Fibrillation

The characteristic irregular pulse of Atrial fibrillation (AF) is described in contemporary reports by physicians from ancient China, India and Greece including Hippocrates and the Chinese Emperor Huang Ti Nei Ching Su Wen. The famous anatomist William Harvey was probably the first to describe “fibrillation of the auricles” in animals in 1628 but the development of the electrocardiograph by William Einthoven in 1900 started the 20th century field of cardiac electrophysiology and enabled Sir Thomas Lewis to record an ECG from a patient in Atrial Fibrillation.

Many of the theories of atrial fibrillation developed in the early 20th century are still relevant today and despite many competing theories of atrial fibrillation development generated from animal research a universal theory of AF development remains elusive. In the late 20th century the development of invasive electrophysiology has led to increased human study of AF with definitive treatments such as catheter ablation that aim to cure the condition.

1.1.2 Atrial fibrillation definitions

Atrial fibrillation is defined by the European Society of Cardiology as

“A cardiac arrhythmia with the following characteristics:

- (1) The surface ECG shows ‘absolutely’ irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern.
- (2) There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.
- (3) The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (>300 bpm).”

International consensus is that there are five types of atrial fibrillation:

- 1) **First diagnosed episode of atrial fibrillation.** This applies to all patients with AF regardless of duration of arrhythmia or severity of symptoms
- 2) **Paroxysmal atrial fibrillation** is self-terminating and lasts less than seven days.
- 3) **Persistent atrial fibrillation** is when atrial fibrillation lasts longer than seven days or termination with drugs or direct current cardioversion
- 4) **Longstanding persistent atrial fibrillation** is when the arrhythmia has lasted longer than one year
- 5) **Permanent atrial fibrillation** is when the arrhythmia has been accepted by the patient and physician and rate control is the definitive management plan.

1.1.3 Epidemiology of Atrial fibrillation

The prevalence of atrial fibrillation increases with age and the impact of atrial fibrillation on an aging UK population has significant socio-economic consequences for the National Health Service. It is one

of the most important public health problems faced by western countries and advances in treatment of cardiac and non-cardiac conditions mean the prevalence and resulting costs will rise.

1.1.1 1.1.4 Prevalence of Atrial Fibrillation

The 2001 ATRIA epidemiological study² in 1.89 million Californian adults suggested an overall prevalence of Atrial Fibrillation of 0.95%. Prevalence increased with age from <0.1% in those under 55 years to 9% in those over 80. The authors projected figures suggested the aging population would result in a 2.5 fold increase in the number of patients diagnosed with atrial fibrillation. A 2007 cross-sectional study from Scotland gave similar results regarding atrial fibrillation prevalence³ however a more recent study from Sweden⁴ has suggested that prevalence of atrial fibrillation may be closer to 3% and the accepted prevalence in international guidelines is a significant underestimate. This underestimate is likely to be due to the difficulty in the diagnosing atrial fibrillation in asymptomatic patients who may represent 10-15% of the AF population⁵.

1.2 Causal factors associated with Atrial Fibrillation development

A number of conditions are associated with the development of atrial fibrillation and in recent years the adjunctive treatment of these risk factors is increasingly recognised as an essential part of the management. This has led to the integrated approach to atrial fibrillation with multi-disciplinary teams used to advise on lifestyle modifications and non-cardiac health interventions⁶. A recent meta-analysis of this approach has shown the promise of these clinics, which, despite their success, remain rare⁷. Condition's that predispose to atrial fibrillation development are described below.

1.2.1 Age

Atrial fibrillation has a strong association with age as seen by the prevalence in the general population. The odds of developing atrial fibrillation increase significantly as people age with the lifetime risk from age forty onwards being 26%⁸. After the age of sixty the prevalence of AF doubles

with each decade and affects almost 10% of patients over the age of eighty. In the over 65 year old population AF is rarely a “lone” condition and usually co-exists with structural or cardiovascular heart disease^{9,10}. The increasing elderly population in the western world, resulting from advances in medical science and the aging of the baby boomer generation, has led to forecasts of an epidemic of atrial fibrillation in the next 10-20 years^{11,12}. While this is not solely down to the effects of age, age allows an accumulation of co-morbidities that increase the likelihood of AF development. The resulting increase in the prevalence of atrial fibrillation in the population is an increasing public health concern.

1.2.2 Gender

Male sex was associated with a 1.5 times greater risk than women of developing AF in the Framingham study¹⁰. The risk of stroke is greater in women¹³ however and this is recognised in the stroke assessment tool the CHADS₂VaSc score where a point is scored for female sex.

1.2.3 Race

Initial population studies looking at the prevalence of atrial fibrillation were limited by a lack of racial diversity and unable to answer whether variations in AF prevalence existed. More recent studies have attempted to address this important question and highlighted significant racial differences^{14,15}. Numerous studies have now demonstrated that AF is less prevalent in individuals of African descent compared to those with European ancestry. One study showed that with every 10% increase in European ancestry there was a 16-20% increased risk of AF¹⁶.

A similar reduction in AF prevalence has been seen in Hispanics and Asians compared to white individuals. In the Multi-Ethnic Study of atherosclerosis, the age and sex adjusted incidence rates per 1000 person years were 11.2 in white populations, 6.1 in Hispanics, 5.8 in African Americans and 3.9 in Asians¹⁷.

It will be important to take into account the racial variation in AF risk in future UK healthcare planning. An appreciation of this difference is needed due to local variations in ethnicity and the inevitable changes that are seen nationally with immigration.

1.2.4 Genetics

It has long been known that AF can recur in families and in the Framingham study a parent with AF was a risk factor for AF development¹⁸. Subsequent analysis demonstrated a 40% increased risk of AF development if a first-degree relative was affected¹⁹. The first genes identified as being associated with AF were a gain of function mutation in the KVNQ1 gene, which encodes for the I_{Ks} potassium channel and the SCN5A gene, which encodes for a sodium channel. The picture has since been shown to be far more complex and the reduction in cost and increasing ease of synthesizing the human genome has resulted in numerous genome-wide association studies. These have demonstrated that AF is a complex polygenetic condition with genes involved in various roles including transcription factors, ion channels, myocytes and cytoskeletal proteins involved. These associations open up the possibility of further study into the mechanisms of AF along with novel and targeted therapies in certain populations²⁰.

1.2.5 Hypertension

In the Framingham study hypertension was an independent risk factor for atrial fibrillation, increasing the risk of AF by 50% in men and 40% in women¹⁰. A population-based case control study of treated hypertensive patients showed a J shaped relationship between average systolic blood pressure and incidence of AF. Interestingly those with a systolic blood pressure of less than 120 mmHg had an increased risk but excluding these led to a roughly linear increase in AF incidence with blood pressure²¹. Analysis of AF incidence in the women's health study also showed increasing incidence of AF with increasing systolic and diastolic blood pressure. Systolic blood pressure was a slightly better risk marker and in this study for every increase of 10 mmHg of systolic blood pressure the incidence of atrial fibrillation the hazard ratio for AF was 1.17 (95% CI, 1.08- 1.27; $p < 0.0001$)²².

The mechanism involved in increasing AF risk with hypertension is unclear, but several factors have been proposed. These include left ventricular hypertrophy, diastolic dysfunction and the effect of renin and angiotensin. These factors have been shown to lead to left atrial stretch, increased wall stress and fibrosis, which are all associated with the development of AF.

1.2.6 Valvular Heart Disease

It is well established that valvular heart disease is associated with the development of atrial fibrillation and increased the risk of AF in the Framingham cohort significantly (Odds ratio 1.8 in men and 3.4 in women)²³. Any structural valvular abnormality is thought to increase the risk of AF development but left sided lesions confer the highest risk, especially rheumatic mitral valve disease where up to 29% of those with isolated mitral stenosis are affected compared to 16% with isolated mitral regurgitation, 52% with mixed mitral valve disease and 1% of those with aortic valve disease²⁴.

1.2.7 Heart Failure

Heart Failure and atrial fibrillation co-exist in up to 42% of patients and share risk factors. Each condition also increases the likelihood of the development of the other²⁵. Women with AF have up to an 11-fold increased risk of developing heart failure while the risk is increased 3 fold for men¹⁰. AF is associated with adverse prognosis in heart failure and a two-fold increase in death¹.

AF Ablation has been associated with positive outcomes in heart failure patients such as exercise capacity²⁶ and improvement in left ventricular ejection fraction²⁷. The CASTLE-AF study, published in 2018, was a large multicentre trial of heart failure patients with ICD's and either paroxysmal or persistent AF. In the study AF ablation was associated with significantly fewer events of a composite

end-point of death and hospitalisation benefit as well as a significant reduction in death from any cause. The beneficial effect was seen predominately in patients in whom the left ventricular ejection fraction was between 25-35%. No benefit was seen in the most severe cases with an LVEF of <25%²⁸.

1.2.8 Obesity

Obesity is a significant risk factor for atrial fibrillation and it has been increasingly recognised over recent years as a modifiable condition that can influence outcomes in atrial fibrillation. It is also associated with sleep apnoea, hypertension and diabetes mellitus, all of which are associated with an increase in AF. A meta-analysis of population based cohort studies by Wanahiti et al demonstrated a 49% increased risk of AF in the obese population and the risk of AF increased in parallel with body mass index²⁹. Obesity is a global epidemic³⁰ and the influence of this is likely to feed into the AF epidemic.

A ground breaking series of studies in Adelaide, Australia by Prash Sanders' group demonstrated that obesity caused structural and electrical changes, cardiac fibrosis and atrial fibrillation in sheep³¹ which was reversed with weight loss³². This led to dedicated weight loss clinics, which ran alongside their electrophysiology service. Weight loss improved outcomes from AF ablation³³ and the loss of ten per cent of body weight was associated with a six-fold increase in sinus rhythm and arrhythmia-free survival³⁴.

The mechanism of obesity on the heart and the development of AF is complex. Several studies have shown an increase in pericardial fat is associated with AF development^{35,36} but the electrophysiological changes, reduced endocardial voltages and fibro-fatty infiltration in the left atrium³⁷ and specifically the left atrial posterior wall are key factors³¹. The predominance of fatty

infiltration in the left atrial posterior wall highlights the role of this area of the heart in the development and perpetuation of persistent atrial fibrillation.

1.2.9 Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) is a condition characterised by periods of breathing cessation during sleep and can be treated with continuous positive airway pressure ventilation (CPAP). It often co-exists with atrial fibrillation and confers a four-fold increase in the development of AF³⁸. Untreated OSA is associated with increased recurrence of AF following AF ablation where as appropriate treatment with the use of CPAP improves outcomes and reduces AF episodes^{39,40}.

1.2.10 Alcohol

The 'holiday heart syndrome' where AF is triggered by a binge of alcohol is a well-known phenomenon⁴¹. Heavy habitual alcohol consumption confers an increased risk of developing AF and for every extra alcoholic drink per day the risk of AF increases by 8%⁴². Those with the highest intake of greater than three drinks per day have the highest risk (relative risk of 1.34 (CI 1.01 – 1.78))⁴³. The impact of low levels of drinking have not been shown to be associated with an increased risk of AF but the difficulty in proving any relationship between AF and low levels of alcohol consumption in those without a previous diagnosis has been highlighted⁴⁴.

Mechanisms proposed to trigger AF by alcohol include autonomic changes such as a hyperadrenergic state and reduced vagal tone^{45–47}. Electrophysiological changes have also been shown to occur with alcohol including prolongation of atrial conduction time⁴⁸ and shortening of refractory periods⁴⁹ following the consumption of alcohol. This combination shortens wavelengths and facilitates re-entry and could allow for the triggering of AF.

1.2.11 Endocrine disease

Diabetes Mellitus is associated with a 1.4-1.6 fold increased risk of atrial fibrillation in population studies^{10,50}. There is significant overlap between co-morbidities such as obesity, hypertension and heart failure with diabetes mellitus. A recent meta-analysis of cohort studies has suggested an increased risk of AF of between 20-28% for those with diabetes. There was a dose-response relationship between increasing blood glucose and AF. It was not able to take into account the effect of obesity and adiposity and these are likely to be significant confounding factors⁵¹.

Thyroid dysfunction is known to increase the risk of atrial fibrillation. Both hypothyroidism and hyperthyroidism have been shown to increase the vulnerability of atrial myocardium to AF in animal models, suggesting a role for stable thyroid function in the maintenance of sinus rhythm⁵².

Hyperthyroidism is a common secondary cause of AF and risk has been shown to increase with decreasing levels of thyroid stimulating hormone as patients become more hyperthyroid. In the same population studies there was a low risk of AF in patients who were hypothyroid^{53,54}. In euthyroid patients TSH levels were not associated with AF, instead increasing free T4 levels increase risk^{55,56}.

A proposed mechanism for hyperthyroidism increasing AF risk is increased B-adrenergic tone and increased automaticity of cardiac myocytes. This leads to increased firing of myocytes that act as AF triggers such as those in the pulmonary veins or elsewhere in the atria⁵⁷.

1.2.12 Exercise

Regular exercise is beneficial for cardiometabolic health and mortality^{58,59}. Regular light to moderate exercise improves cardiovascular health and therefore reduces the risk of AF⁶⁰. In a cohort study of over 12000 patients who had undertaken treadmill testing at the Mayo clinic, and followed up for a

median of 14 years, physical fitness was associated with reduced risk of AF, stroke and mortality. For those patients with AF cardiorespiratory fitness was inversely related with stroke and mortality⁶¹.

These beneficial effects of exercise are slightly offset by the increased risk of atrial arrhythmias in endurance athletes^{62–64}. The increased risk may be as much as 8 fold by middle age for men who undertake regular intensive endurance⁶⁵. There is a lack of data regarding the effects of endurance exercise in women and the possibility of gender specific differences in risk mean further study is clearly needed^{66,67}. Similar atrial structural remodelling is seen in response to exercise in both genders but women have smaller right atria and increased myocardial deformation compared to men who are similarly conditioned⁶⁸.

A number of mechanisms are proposed to explain the increased risk of AF in endurance athletes. Exercise increases left atrial pressure, atrial volumes and P wave duration^{68,69}. Further proarrhythmic changes in the atrial substrate are seen with exercise including myocardial fibrosis and myocardial inflammation, increasing atrial premature beats and increased vagal tone leading to bradycardia and decreased atrial refractoriness^{70,71,72}.

1.3 Clinical sequelae and Prognosis

Atrial Fibrillation is associated with increased mortality in the Framingham heart study with between a 1.5 and 1.9 fold increase in mortality when adjusted for pre-existing cardiovascular conditions. At 10-year follow-up 61.5% of men with AF between the ages of 55 and 74 years of age had died compared with 30% of those without AF. In women it was 57.6% for those with AF versus 20.9% without. For patients without concurrent cardiovascular disease AF was associated with a two-fold risk of death¹.

A meta-analysis of 104 studies involving over 9 million patients by Odutayo et al showed that AF was associated with an increased risk of all-cause mortality (Relative risk 1.46), cardiovascular mortality (2.03), major cardiovascular events (2.03), stroke (2.42), ischaemic stroke (2.33), ischaemic heart disease (1.61), sudden cardiac death (1.88), heart failure (4.99), chronic kidney disease (1.64) and peripheral arterial disease (1.31)⁷³.

Given increased risk of death, cardiovascular and renal disease seen in epidemiological studies it should follow that suppression and treatment of atrial fibrillation should confer a mortality benefit. This has as yet proved difficult to prove in randomised controlled trials however. In the AFFIRM study no mortality benefit was seen when comparing rate versus rhythm control although this study highlights the difficulty of study in AF where at any one time one third of the rate control arm were in sinus rhythm compared to two thirds of the rhythm control arm⁷⁴. Re-analysis of AFFIRM highlighted the importance of anticoagulation on mortality in AF while sinus rhythm was associated with a mortality benefit but this was negated by the use of antiarrhythmic medications⁷⁵, the mortality risks of which are well recognised^{76,77}.

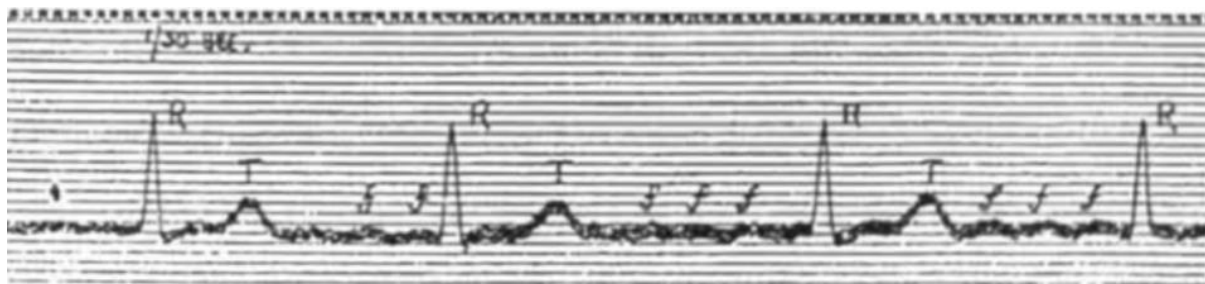
Studies of catheter ablation for Atrial Fibrillation with a control arm of rate control have proved difficult to conduct for a variety of reasons. The necessary size of study to demonstrate statistical significance for mortality as well as the problem of randomising patients to a non-catheter ablation arm mean that the mortality benefit of a rhythm control strategy remains unproven outside of heart failure populations^{78,79}.

1.4 Pathophysiology of Atrial Fibrillation

A universal theory for the pathophysiology of atrial fibrillation remains elusive but many of the theories regarding the pathophysiology of atrial fibrillation remain as relevant today as they did in

the early 20th century. The exact mechanism causing atrial fibrillation is complex and unclear, but it is widely accepted that arrhythmia onset requires a trigger and a substrate to maintain the arrhythmia. Over the past 100 years three main theories have persisted to explain the mechanism of onset for atrial fibrillation. These are: Ectopic Foci, Multiple propagating wavelets and localised re-entrant activity with fibrillatory conduction.

Figure 1-1 An ECG recording made by Thomas Lewis from a patient with atrial fibrillation with fibrillatory “f” waves highlighted⁸⁰



1.4.1 Ectopic Foci

Rothberger and Winterberg were the initial proponents of the theory that atrial fibrillation is triggered by rapid discharge at an isolated ectopic foci. Their research, published just before Thomas Lewis produced the first ECG showing atrial fibrillation, demonstrated atrial fibrillation triggered by a 50Hz burst at a single location in the atrium⁸¹. However contemporaneous research into the mechanism of AF by Lewis⁸², Mayor⁸³, Mines⁸⁴ and Garrey^{85,86} led to the circus movement theory, which superseded ectopic foci theory and became the accepted mechanism for the first half of the twentieth century⁸⁷.

In 1949 doubt was cast on the generally accepted theory by Scherf and Terranova who were able to induce atrial tachycardia and fibrillation by applying Aconitine (a sodium channel antagonist) to the epicardial surface of a canine right atrial appendage^{88,89}. This led to a number of research papers that backed up the ectopic foci theory, although it was debated whether the mechanism for impulse formation at the focus was due to repetitive discharges or localised circus movement⁹⁰⁻⁹³.

It was almost half a century later in 1998 when the ground-breaking series by Haissaguerre et al demonstrated an ectopic trigger for AF in the pulmonary veins that could be eliminated by focal ablation⁹⁴. This work started a huge escalation in cardiac electrophysiology and the invasive treatment of AF targeting these causative triggers.

1.4.2 Circus Movement and the Multiple Wavelet Theory

The circus movement theory of AF was the accepted mechanism and widely taught as such until the late 1940's after being described by Thomas Lewis in early 1920's^{87,95}. The theory was generated from work done over the previous thirty years by a number of researchers beginning with Engelmann in 1896 who suggested AF was due to multiple heterotopous foci. It was Mayor in 1906 experimenting on jellyfish and rings of muscle from the ventricles of turtles who showed that by applying combinations of electrical impulses a sustained electrical wave would propagate indefinitely in one direction⁸³. These experiments were repeated and refined by Mines and Garry before being incorporated by Thomas Lewis into his circus movement theory of AF. Mines described the basic requirements for initiation and maintenance of re-entry to be: unidirectional conduction block, a core of inexcitable conduction tissue around which the wave can propagate and excitable tissue ahead of the wavefront⁸⁴⁻⁸⁶.

Thomas Lewis's description of the mechanism of atrial flutter and fibrillation proposed a single circuit generating fibrillatory activity. In atrial flutter there was a large circuit around the right atrium and Lewis postulated the path length around the auricle of a great vein was greater than the wave length and this would accurately repeat from cycle to cycle as the wave revolves around the large obstacle and the wavefront follows some distance behind the tail. For atrial fibrillation the circuits were smaller with smaller path length and shorter excitable gap. In this scenario the wavefront of

electrical activity follows closely behind its own tail giving rise to atrial excitation cycles that follow closely together and if the refractory period in the surrounding atria is shorter the propagation of the waves to the atria will become disorganised and lead to AF.

Work in the 1940's by Weiner and Rosenblueth further refined the circus movement theory, postulating the rotation around single or multiple obstacles was necessary to initiate and maintain atrial arrhythmia⁹⁶. Gordon Moe moved things forward again. Moe's work in the 50's was based on the theory that atrial activity was totally disorganised and 'randomly wandering wave fronts, ever changing in number and direction'. This led to the multiple wavelet hypothesis of AF and the first computer models of AF which predicted the randomness in temporal and spatial distribution of membrane properties which played dominant roles^{97,98}.

Allessie et al in 1985 used animal models to map the spread of excitation and AF following rapid atrial pacing in the presence of Acetylcholine. They demonstrated multiple propagating wavelets but the number needed to sustain the arrhythmia was between 4 and 6 rather than greater than 26 as Moe's computer model had predicted⁹⁹. The same group had previously demonstrated that sustained vortices of re-entry could occur in healthy tissue in the absence of an anatomical obstacle, a finding that went against Mines basic requirement for re-entry¹⁰⁰.

1.4.3 Rotor Theory

Rotor theory evolved from the previous experimental work that predicted the heart could sustain electrical activity that rotated around a functional obstacle. Davidenko *et al* first demonstrated that self-sustaining rotor waves could be introduced by a single premature electrical stimulus¹⁰¹. A rotor is an organizing source and driver of functional re-entry activity and these rotors can be shown to emit a 2D wave of excitation. Unlike the leading circle theory of fibrillation development where the

structural or functional obstacle is fixed, refractory and static computer models of rotors show how they are not fixed around an anatomical or functional point and do not have a fixed wavelength. They therefore pivot and rotate around a moving excitable core allowing them to drift and meander depending on the tissue excitability¹⁰².

Rotor theory brings us back 100 years to Thomas Lewis's initial observations that a single circuit can maintain and generate fibrillatory activity except rather than being waves around a ring they may be spiral waves around rotors. Low density mapping studies in humans using basket catheters reinforced this theory and suggested stable rotors as drivers of AF which could be targeted with ablation^{103–105}. High-density atrial mapping studies have not supported the basket catheter mapping studies. Instead rotors have either not been seen^{106,107} or existed only briefly^{108,109}. Further doubt about the role of stable rotors in the persistence of AF has been cast by the relatively poor outcomes of independent investigations using basket catheters to target rotors in AF ablation^{110,111}.

1.4.4 The elusive universal theory of Atrial Fibrillation

After over 100 years of study in atrial fibrillation the pathophysiology remains mysterious and a question that will generate hypotheses for years to come. It is clear from Haisseguerres work and the subsequent twenty years of AF ablation that ectopic foci are key in selected patients with AF. Yet persistence of atrial fibrillation maintained by swirling electrical vortexes similar to the circus movement theory has repeatedly been shown in computer models and mapping studies. Further to that endo-epicardial currents have been shown to have a demonstrable role in focal activation and perpetuation of AF^{106,112}.

The development of atrial fibrillation is caused by structural and electrical changes in the atria. These can be associated with co-morbidities or just as a consequence of age or genetic susceptibility. All the theories of atrial fibrillation may be true and co-exist occurring in some AF patients but not others or all AF patients at some time depending on the AF syndrome. This variety of potential mechanisms presents a clinical challenge to treating AF. Ablation can target triggers, substrate or both. However without fully understanding why AF occurs it is perhaps unsurprising that the optimal ablation lesion pattern is undefined.

1.5 Management of atrial fibrillation

The management of atrial fibrillation consists of two components. One is the assessment of stroke and thromboembolic risk with anticoagulation instituted if indicated; this is done in all patients. The other decision is rate or rhythm control strategy. This is where AF is either accepted or alternatively, in appropriate individuals, AF is suppressed or treated via drugs or catheter ablation.

1.5.1 Thromboprophylaxis and Stroke Risk

As Atrial fibrillation increases an individual's risk of stroke five-fold consideration of anticoagulation should be made in every patient. AF related strokes are often more severe and associated with greater mortality, morbidity and consequent costs. It has been estimated that the societal costs of stroke in the UK are £8.9 Billion per year and by improving AF detection and treatment significant public health improvements can be made with consequent reduction in stroke-related costs. The Imperial College Health Partners model of AF can be used to estimate AF prevalence, undiagnosed AF and undertreated AF for individual CCG's (clinical commissioning groups) using publicly available primary care data. It can also be used to calculate the potential strokes prevented and total cost saved by better screening and anticoagulation. For Somerset CCG (where I work) with a population

of 561,000 estimates from the calculator suggest 16.9% of AF patients are not diagnosed, 28.7% of those with AF have not been appropriately risk assessed, 18.7% have been risk assessed but are not appropriately anticoagulated and 20% are undertreated. If these care deficiencies are corrected reductions strokes could save over £10 million in costs over 3 years. Similar inadequacy of identification and screening are seen throughout the UK and Public Health England have launched a program to reduce the incidence of AF related strokes by 5000 in the next 5 years.

1.5.2 Risk Scores

While AF increases the risk of stroke and thromboembolism up to five-fold this is greatly influenced by age, sex and co-morbidity. The CHADS₂VaSc score is a risk score that given an estimate of annual stroke risk.

- C – Congestive Heart Failure – 1 (point)
- H – Hypertension – 1
- A – Age ≥ 75 – 2
- Diabetes Mellitus – 1
- Stroke History – 2
- Vascular disease – 1
- Age ≥ 65 – 1
- Sex category - 1

The CHADS₂VASc score increased the accuracy of the existing CHADS score and identified a group of patients with a score of 0 in men or 1 in women who are truly low risk and do not require anticoagulation¹¹³. The HASBLED score can be used in conjunction to estimate bleeding risk and identifies risk factors that can be modified¹¹⁴.

1.5.3 Rate versus Rhythm Control

The other key strand in the management of AF is a decision about rate or rhythm control. This is a decision about whether the focus of treatment should be to accept AF and just control the

ventricular rate or to prevent episodes of AF and maintain sinus rhythm. Despite AF being associated with increased mortality a rhythm control strategy has not been shown to improve mortality outside of heart failure populations. Therefore the decision for rhythm control remains driven by symptoms from atrial fibrillation.

1.5.4 Anti-Arrhythmic Medication

Anti-arrhythmic drugs are given to patients with atrial fibrillation to maintain sinus rhythm. They are classified by the Vaughan-Williams classification into four classes. Of these the class I drugs flecainide, procainamide, disopyramide the class III drug Sotalol and the class IV drug amiodarone are used most commonly depending on the patient characteristics and presence or absence of ischaemic or structural heart disease. While they can be effective, all the anti-arrhythmic drugs are pro-arrhythmic and carry a degree of morbidity¹¹⁵. They have consistently been shown to be inferior to catheter ablation for the prevention of AF (table 1.1)

1.5.5 Direct Current Cardioversion

Direct current cardioversion has been used to terminate episodes of atrial fibrillation since the 1960s. It is simple, safe and widely available but long-term sinus rhythm is rarely achieved through cardioversion alone¹¹⁶. Generally the procedure is used for AF patients with acute haemodynamic instability or as a trial of sinus rhythm to assess symptomatic improvement for those in persistent atrial fibrillation. Elective cardioversion outcomes are worse with increasing durations of atrial fibrillation and larger left atrial dimensions¹¹⁶. Acute success of cardioversion and maintenance of sinus rhythm after the procedure can be improved with pre and post procedural amiodarone use^{117,118}. Patients who undergo successful cardioversion with a symptomatic improvement need consideration for anti-arrhythmic medication or catheter ablation.

1.5.6 Atrial Fibrillation Ablation

In 1998 Michelle Haseguire et al identified a cohort of patients with paroxysmal atrial fibrillation in whom spontaneous initiation of AF was mapped to triggers in the pulmonary veins which could be targeted by focal ablation at these sites¹¹⁹. This built on a previous case series¹²⁰ and they then developed the technique of pulmonary vein isolation, demonstrating that Atrial fibrillation can be successfully treated by ablation. This development marked the birth of modern AF management. AF ablation with PVI is now the cornerstone of treatment for patients with symptomatic drug resistant AF and has widespread inclusion in guidelines on the management of AF¹²¹.

Pulmonary vein isolation involves accessing the left atrium via an atrial trans-septal puncture and creating a ring of inert scar tissue encircling the pulmonary veins so the triggers of AF cannot escape from the pulmonary veins. The lesions can be created using several different technologies: Radiofrequency (RF) ablation (delivered as a series of adjoining points inside the atrium via linear or circular catheters that encircle the pulmonary veins), cryoablation or laser ablation via balloons advanced into the pulmonary veins. The ablation technique utilised to achieve PVI is at the discretion of the operator as no technology has been shown to be superior. In the randomised control trial FIRE and ICE cryoablation was non-inferior to RF ablation¹²².

Outcomes of AF ablation for paroxysmal AF remain excellent with freedom from AF rates off anti-arrhythmic drugs at one year greater than 70% in several studies of PVI via RF ablation or cryoablation¹²³.

Improvements in hard endpoints such as mortality are as yet unproven for AF ablation outside of heart failure populations in the CASTLE AF study²⁸.

The recently published CABANA study^{124,125}, randomised patients to AF ablation or medical therapy. This landmark study's first results were presented in 2017 and no significant difference in a composite endpoint of death, disabling stroke, serious bleeding or cardiac arrest was seen overall. When re-analysed as treatment received rather than per-protocol a difference was seen. This analysis introduces bias as these treatments are against randomisation potentially leaving the comparative groups unmatched. Overall 2204 patients were randomised, 1108 to ablation and 1096 to medical therapy however only 90.8% of those randomised to ablation received that treatment and 27.5% of those in the medical therapy arm received ablation. What was significant and in keeping with previous studies is that ablation significantly reduced AF recurrence compared to medical therapy. A lower than expected event rate left the trial underpowered however and this much anticipated study did not answer the question about AF ablation for mortality benefits.

Following the 2017 ORBITA study of angioplasty which included a sham arm¹²⁶, as have studies of renal denervation¹²⁷. There have been calls for future AF ablation studies to be placebo controlled and include a sham arm where a fake procedure is performed¹²⁸. This would add weight to the benefit of AF ablation for symptomatic AF.

Table 1-1 Summary of trials of AF ablation for PAF

Trial	Yr	Study type	Number	Timeframe	Ablation success	Drug success	Ablation complications
RAAFT ¹²⁹	2005	AAD vs PVI	70	12 months	84%	37%	9%

APAF ¹³⁰	2006	AAD vs PVI + mitral & tricuspid line	198	12 months	86%	22%	1%
A4 Study ¹³¹	2008	AAD vs PVI + optional additional ablation	112	12 months	89%	23%	5.7%
Thermacool AF ¹³²	2010	AAD vs PVI (optional CFAE + Lines)	167	12 months	66%	16%	4.9%
STOP-AF ¹²³	2013	AAD vs PVI (cryoballoon)	245	12 months	70%	7%	3.1%
RAAFT -2 ¹³³	2014	AAD vs PVI + optional non-PVI triggers	127	24 months	45%	28%	4.9%
CABANA ¹²⁵	2019	AAD vs PVI + (optional additional ablation)	2204	48.5 months	MACE - 8.0% Mortality – 5.2%	MACE -9.2% (p = 0.3) Mortality – 6.1% (p=0.38)	6.9%

1.5.7 Limitations of Atrial Fibrillation studies

Interpreting the success rate from atrial fibrillation ablation studies can be challenging. Often the earlier studies are in mixed groups of paroxysmal, persistent and long-standing persistent AF patients. Likewise, while the lesion set is usually based around pulmonary vein isolation, additional lesions such as CFAE (complex fractionated atrial electrograms) or linear ablation are at the discretion of the operator. This can make studies in AF heterogeneous and difficult to draw conclusions from. In addition to this, technological changes in left atrial mapping and ablation catheters mean that earlier studies are not always insightful when assessing modern AF ablation. Significant variation also exists in follow-up of AF ablation patients as the more we look for arrhythmia following ablation the more we are likely to find it. Time and economic constraints preclude regular ambulatory monitoring during follow-up or the routine implantation of loop

recorders. The variability in recruitment, trial design and follow-up led to international guidelines on research in AF¹³⁴.

1.5.8 Ablation for Persistent Atrial Fibrillation

As AF ablation became widespread it became clear that outcomes in patients with persistent atrial fibrillation were inferior to those in paroxysmal AF. In longstanding persistent atrial fibrillation ablation outcomes are particularly poor. Additional ablation targeting non-pulmonary vein triggers such as complex fractionated electrograms, rotors and ganglionic plexi or additional substrate modification via left atrial roof, floor and mitral isthmus lines have been used in patients with persistent AF. Despite this increasing complexity of ablation, outcomes have not significantly improved and pulmonary vein isolation remains the mainstay of AF ablation.

1.5.8.1 Additional Linear ablation

The addition of linear ablation to pulmonary vein isolation is intended to reduce the risk of atrial arrhythmia recurrence by preventing the development of macro re-entrant flutter. The commonest additional lesions are a mitral isthmus line or a roof line connecting the pulmonary veins. Small studies by Ernst, Jais and Fassini suggested improved outcomes with linear ablation combine with PVI over PVI alone^{135–137}. However linear ablation showed no benefit over PVI alone in the STAR AF II trial in persistent AF¹³⁸. A meta-analysis of linear ablation added to PVI by Scott et al which includes STAR AF II showed no significant difference in arrhythmia free survival and highlighted the increased procedural duration and fluoroscopy time with additional ablation lesions¹³⁹.

1.5.8.2 Complex fractionated atrial electrogram ablation

Complex fractionated atrial electrograms (CFAE) ablation was first described by Nademanee in 2004¹⁴⁰. CFAE's were described at areas of slow conduction where wavelets rotate around pivot

points¹⁴¹. The idea behind CFAE ablation is to target areas of functional re-entry that could act as triggers for AF. CFAE were described by Nademanee as either¹⁴⁰:

- 1) atrial electrograms that have fractionated electrograms composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period
- 2) atrial electrograms with a very short cycle length (≤ 120 ms) averaged over a 10-s recording period

The initial study outcomes were good in a mixed AF population (57 PAF, 64 PsAF) with 74% free from AF at 1 year. PVI was not performed but many of the CFAE were mapped to the pulmonary vein ostia. Subsequent study in a persistent AF population resulted in only 33% freedom from AF at 14 months following a single procedure¹⁴². In the STAR AF trial CFAE ablation alone was inferior to PVI + CFAE¹⁴³ and the addition of CFAE to PVI did not improve outcomes in persistent AF ablation in STAR AF II¹³⁸

1.5.8.3 Rotor ablation and FIRM mapping

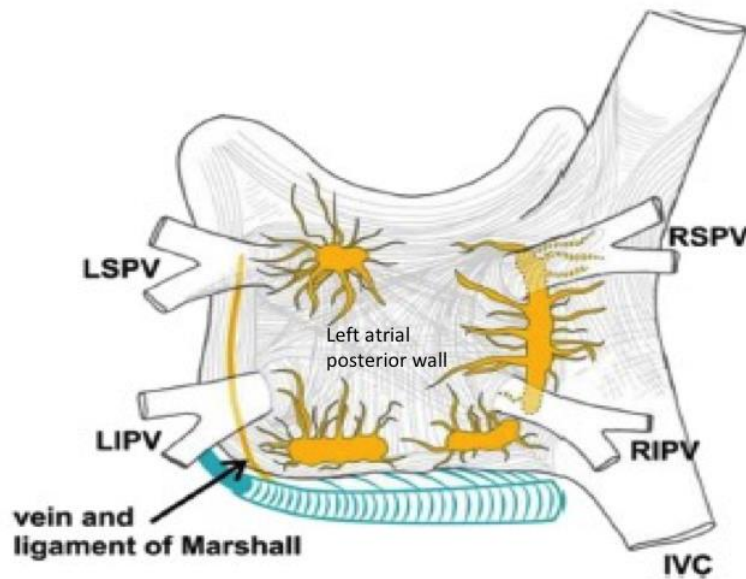
Great excitement was generated by the results published by Narayan et al in 2012 of a study comparing basket catheters and Focal Impulse and Rotor Modulation (FIRM) guided ablation with conventional ablation. In 92 patients, of whom 72% had persistent AF, those who underwent FIRM-guided ablation had significantly superior freedom from AF (82.4% vs 44.9%, $p < 0.001$)¹⁰⁴. The long term outcomes were similarly impressive¹⁴⁴. However the results have not been reproduced by other groups^{110,111} and concerns have been expressed about the generation of the rotor maps as the signal processing algorithms have not been made available by the manufacturer¹⁴⁵. Currently the efficacy of FIRM ablation in persistent AF is unproven.

1.5.8.4 Ganglionic Plexi Ablation

The intrinsic cardiac nervous system consists of ganglionic plexi (GP) located epicardially on the posterior wall of the left atrium¹⁴⁶. Ganglionic Plexi have been implicated in both the triggering and

perpetuation of atrial fibrillation¹⁴⁷. Inadvertent ablation of GP during standard catheter ablation of atrial fibrillation may occur due to the location of GP near the pulmonary veins but it has also been shown that targeting GP during ablation can enhance procedural success¹⁴⁸ with the presence of GP responses post AF ablation being a predictor of worse outcomes¹⁴⁹.

GP can be targeted either through anatomical maps¹³⁴ or through identification of GP by high frequency stimulation¹⁵⁰. A number of surgical studies have shown that freedom from AF is improved by epicardial targeting of GP sites¹⁵¹. These can be excised or ablated. In one study botulinum toxin injected into these sites reduced AF occurrence^{152,153}. Active GP sites following surgical ablation are associated with AF recurrence¹⁵⁴

Figure 1-2 Anatomical map of Ganglionic Plexi (adapted from Calkins et al¹³⁴)

LSPV- left superior pulmonary vein, RSPV –right superior pulmonary vein, LIPV – left inferior pulmonary vein, RIPV right inferior pulmonary vein, IVC – inferior vena cava

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In catheter ablation targeting GP alone has not shown sufficient promise to be adopted widely with outcomes inferior to PVI^{155–157}. However the addition of endocardial mapping and ablation of GP to PVI has been shown to be superior to either PVI or GP ablation alone in paroxysmal¹⁵⁸ and persistent AF¹⁵⁹. Superior outcomes in redo ablation have been shown with the addition of GP ablation when compared to redo PVI alone¹⁶⁰. Improved outcomes with the addition of GP ablation to surgical AF ablation mean it will remain a potential adjunct to PVI for the treatment of AF¹⁵¹.

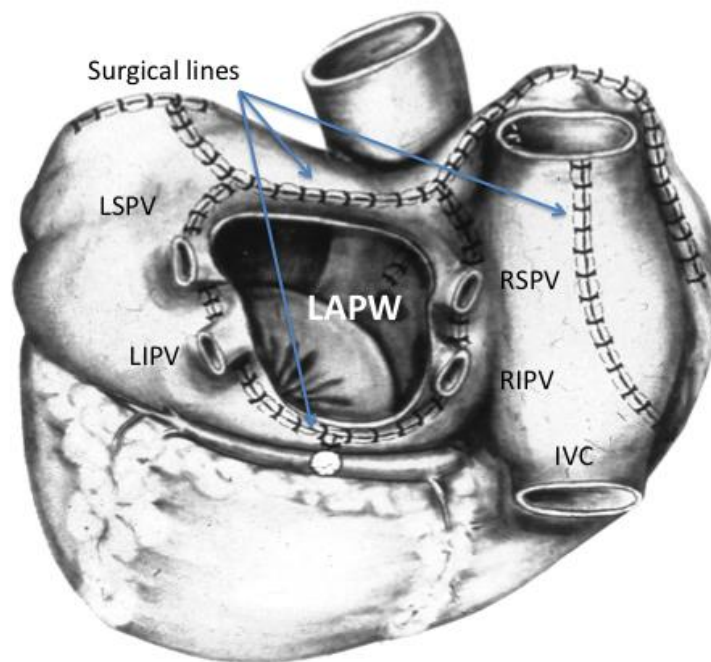
1.6 Surgical AF ablation

1.6.1 Surgical AF ablation techniques

Several techniques for surgical treatment were developed in the 1980's, which included the left atrial isolation procedure, the corridor procedure, the atrial transection procedure and the maze procedure. Of these the Cox-Maze became the standard¹⁶¹.

1.6.2 The Maze procedure

First performed by James Cox in 1987, the MAZE procedure built on AF mapping and modelling studies by Moe⁹⁸ and Allessie⁹⁹ and his own research on computer and animal models of atrial fibrillation. As previously described, according to these model's atrial fibrillation, once established, consisted of two or more large simultaneous macro re-entry circuits in the atria simultaneously. It was deduced that by placing the atrial lesions close together these circuits could not develop but dividing the atria up into small strips while treating atrial fibrillation prevented atrial activation during sinus rhythm. The Maze lesion set was designed to break up the atria sufficiently to prevent atrial fibrillation but not enough to inhibit conduction in sinus rhythm¹⁶². The lesion set divided up the atrium to prevent macro re-entry circuit development with a main corridor that allowed normal atrial conduction. A series of blind alleys off this corridor allowed conduction to all parts of the atrium but prevented circuit formation. Initially developed on cadaveric canine hearts it was then used in live animal models before the first human operation in 1987.

Figure 1-3 The first MAZE lesion set¹⁶³

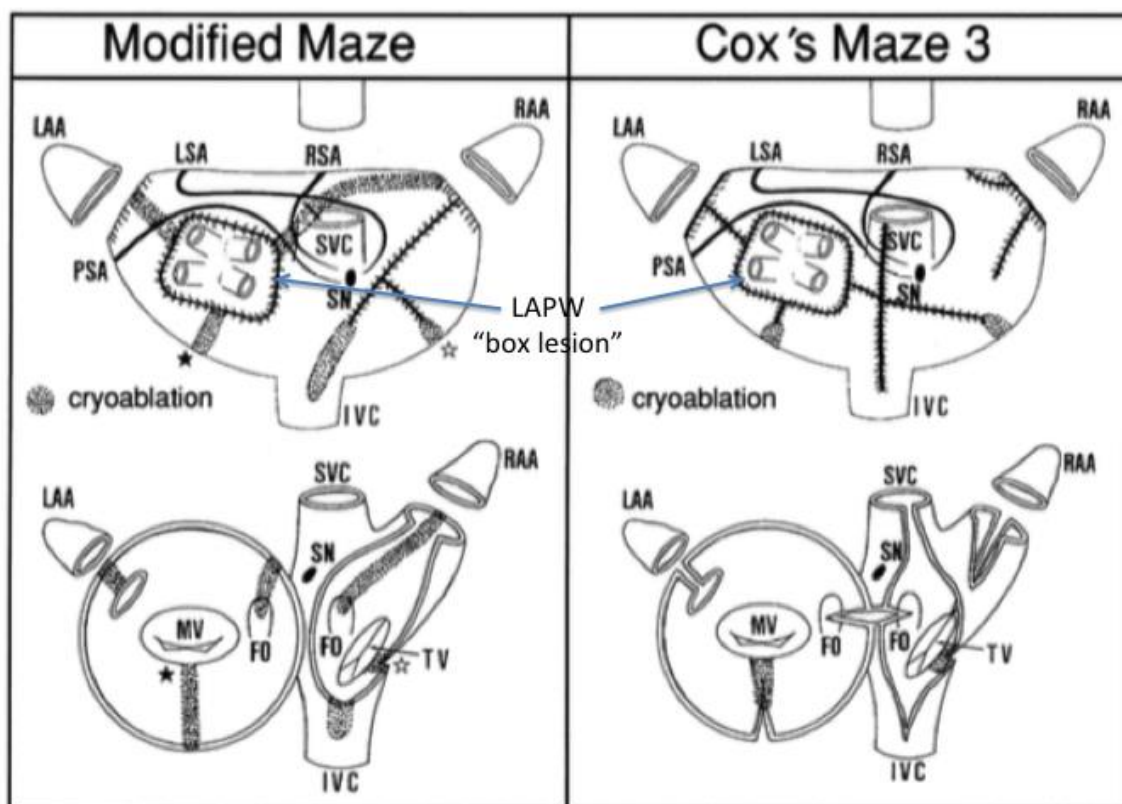
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The first man who underwent the MAZE remained in sinus rhythm for seven days postoperatively until the atrial fibrillation recurred. At this point he was commenced on digoxin and procainamide and reverted to sinus rhythm. This was maintained for almost twenty years despite the early discontinuation of procainamide due to the development of drug-induced lupus. The second patient who underwent a Maze procedure five months later was George Dheere, a 37-year-old pilot from Cyprus. He had previously undergone an atrial transection procedure, which meant the final lesion set was similar to the later Maze III lesion set. He developed an atypical atrial flutter shortly after surgery which was mapped to the mitral isthmus and successfully treated with endocardial catheter fulguration¹⁶³.

1.6.3 Maze III procedure

The Cox-Maze III procedure was developed from the original maze procedure following the atrial dysfunction and high incidence of late chronotropic incompetence that necessitated pacemaker implantation in the initial maze patients. A maze II procedure with a revised lesion set aimed to improve atrial conduction but this was a technically challenging procedure with similar drawbacks to the maze I. This led to the maze III procedure; also known as the “cut and sew” maze which for two decades was the gold standard for surgical AF ablation. Isolation of the left atrial posterior wall with a box lesion incorporating the pulmonary veins is key in this lesion set.

Figure 1-4 The Modified Maze and Maze III lesion sets used in a Japanese series of convergent procedures (adapted from Kosakai et al¹⁶⁴)



1.6.4 Outcomes from the Cox-Maze III “cut and sew” procedure

The results of the Maze III procedure have been excellent. In James Cox’s original series of 112 consecutive patients at Washington University, St Louis, late follow-up was available in 88% of patients in whom 96% were free of atrial fibrillation at a mean of 5.4 +/- 3.0 years and of those in whom 14 year follow-up was available 92% remained free from symptomatic AF with 80% off anti-arrhythmic drugs¹⁶⁵. Further large series at the Cleveland and Mayo clinics both demonstrated success rates of 90% in restoring sinus rhythm and 90% remained in sinus rhythm after 3 years follow-up in the Cleveland series^{166,167}.

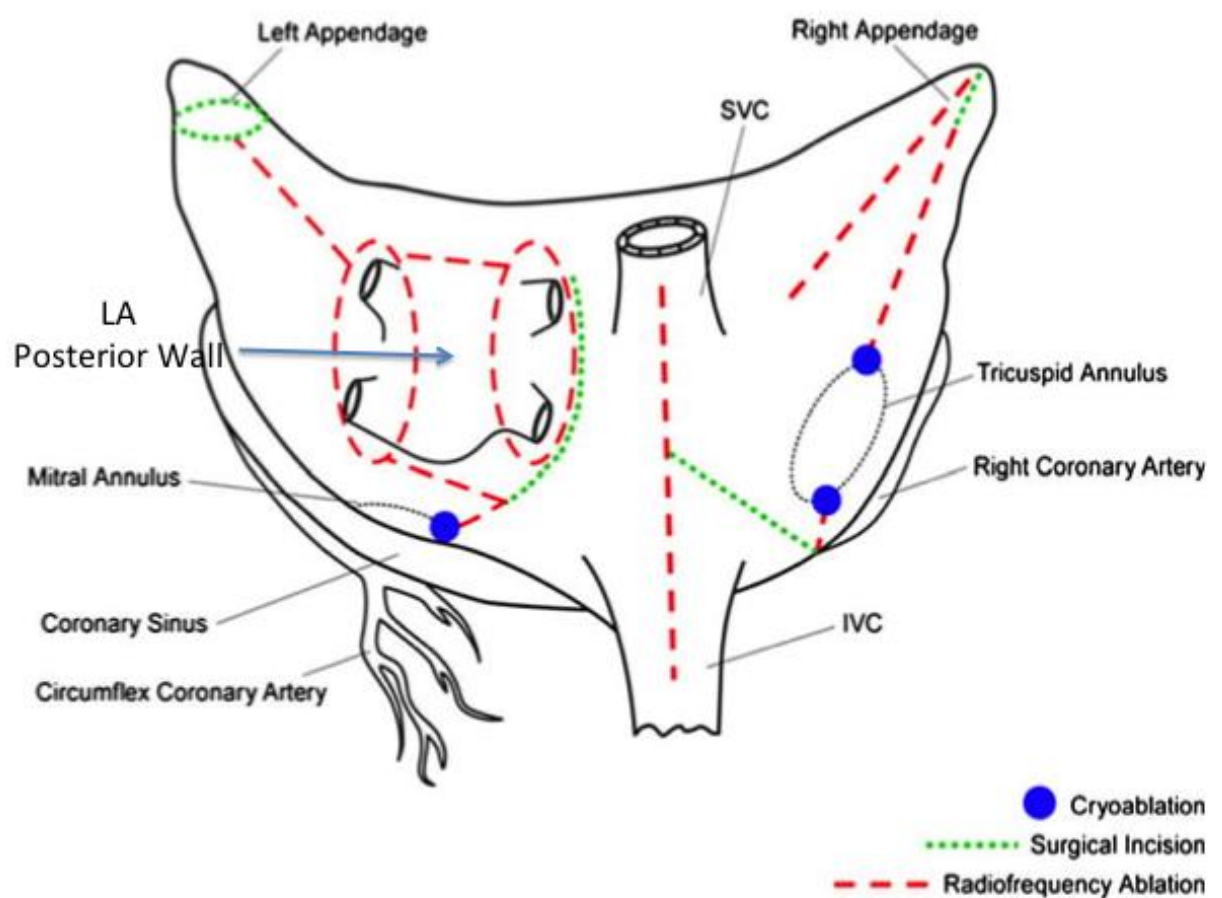
Despite its apparent efficacy the Cox-Maze III procedure was limited by its complexity, long cardiopulmonary bypass duration and need for a median sternotomy. Uptake of the procedure was limited to patients undergoing concomitant heart surgery as it was deemed to be too invasive for standalone AF treatment¹⁶⁸.

1.6.5 The Cox-Maze IV

The Cox-Maze IV procedure was designed to replicate the maze III with the use of ablative tools rather than via a “cut and sew” technique. This was advantageous as the lesion set was simpler and could be performed through either a median sternotomy or right mini-thoracotomy for standalone AF surgery. The Cox-Maze IV was developed in 2002 and utilised ablation technologies to deliver the modified lesion set¹⁶⁹. The simplification of the operation led to significant expansion in surgical atrial fibrillation ablation. Procedural time, cross-clamp time and complications such as peri-operative stroke are reduced compared to the Cox-maze III^{170,171}. Further reductions in morbidity and hospital stay are seen with the mini-thoracotomy compared to a median sternotomy approach¹⁷².

In a single centre study of over 20 years experience with the Cox-Maze III and IV by Weimar et al the major complication rate of the CM – III was 10% and 1% with the CM – IV, A similar rate of pacemaker implantation was seen with the two procedures at 8% and 7% respectively. The 30 day mortality rate for CM – III was 1.8% and 1% for CM IV¹⁷¹.

Figure 1-5 Cox Maze 4 lesion set adapted from Ruaengsri et al¹⁷³



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Outcomes of the Cox-Maze IV are good with 5 year freedom from AF 78% on anti-arrhythmic drugs and 66% off AAD's in a large series of 576 patients at Washington University. In this study there was no statistical difference in outcomes between paroxysmal and persistent atrial fibrillation if those who did not have an intact "box" lesion set were excluded. Failure to isolate the left atrial posterior wall and complete a "box" was associated with worse outcomes¹⁷⁴. In a cohort of patients with AF who underwent a concomitant Cox-Maze IV during coronary artery bypass grafting outcomes at 5 years were similar¹⁷⁵.

1.6.6 Minimally invasive surgical Atrial Fibrillation ablation

The use of surgical catheter ablation in the Cox-Maze IV led to minimally invasive thoracoscopic techniques for AF ablation that could be performed off cardio-pulmonary bypass using video assisted thoracoscopy (VATS). These techniques utilise radiofrequency, microwave or hi-frequency ultrasound (HIFU) energies. The lesion set is based on the Cox-maze and the central lesion set involves isolating the pulmonary veins and left atrial posterior wall.

The microwave system used in the early 2000's was less than satisfactory with freedom from AF only 42% at one year in a series by Pruitt¹⁷⁶. HIFU was equally disappointing¹⁷⁷ and radiofrequency has become the predominant ablation energy for minimally invasive AF ablation. Monopolar ablation through a unilateral thoracoscopic approach is attractive as it should in theory reduce complications compared to a bilateral approach with bipolar RF clamps. Freedom from AF with the monopolar approach has been shown to be up to 89% on ADD and 51% without^{178,179}.

With bipolar radiofrequency ablation through bilateral thoracotomies freedom from AF off AAD varied from between 86%¹⁸⁰ and 51%¹⁸¹ at one year in mixed AF populations. The heterogeneity of series of minimally invasive surgery make interpretation of the techniques difficult to assess. One head to head study has suggested a potential benefit for minimally invasive surgical ablation over catheter ablation but at a cost of significant increase in adverse events¹⁸².

Research continues on the optimal approach for AF and surgical ablation. The multi-disciplinary approach of surgical and electrophysiology expertise in AF ablation led on from minimally invasive surgery to combine surgical and electrophysiological procedures either performed as one single procedure or as two separate staged procedures. Both surgical and hybrid ablation have been given a IIa recommendation for patients with AF in the most recent guidelines.

1.7 Hybrid AF ablation

The first Cox-Maze surgical technique is now 30 years old and long-term outcomes of this and the subsequent Cox-Maze III procedure remain excellent^{161,183–185}. The development of the Cox-maze IV technique in 2004, which could be performed without cardio-pulmonary bypass, allowed consequent shorter recovery times and fewer complications but failed to match the Cox-maze outcomes. This led to hybrid ablation techniques incorporating either simultaneous or staged electrophysiological study¹⁷⁴.

The heterogeneity of previous hybrid ablation series and difficulty in interpretation of their results has been highlighted in recent reviews^{186,187}. At date of publication three techniques for hybrid ablation have been reported. These include the thoracoscopic encircling catheter, the bilateral clamp technique and the convergent subxiphoid pericardioscopic procedure. Of the published studies most are in heterogeneous populations of paroxysmal, persistent and long-standing

persistent patients and interpretation of outcomes needs to take this into account. For the bilateral clamp technique, 12 month freedom from AF symptoms off anti-arrhythmic drugs in all AF syndromes between 91%¹⁸⁸ and 88.1%¹⁸⁹. Several studies of the bilateral clamp report similar outcomes with less than one-year follow-up. Outcomes for persistent and long-standing persistent atrial fibrillation in the bilateral clamp studies are good with up to 88.2%¹⁸⁹ and 87.7%¹⁹⁰ freedom from AF symptoms off anti-arrhythmic drugs.

The previous studies of a monopolar previous iteration of the thorascopic encircling catheter produced widely differing outcomes. In Le Meir's series of 19 patients, only 7/19 (36.8%) of all AF patients and 4/14 (28.6%) of persistent AF patients remained arrhythmia free at one year¹⁹¹. In comparison Bisleri et al report 40/45 (88.9%) of persistent atrial fibrillation patients remained free of symptomatic arrhythmia at one year. The same group had also previously reported 30 patients with outcomes of 87.5% remaining arrhythmia free¹⁹².

There have been three published studies of the sub-xiphoid approach and all of these have been performed as convergent procedures. A mixed cohort of patients with different AF syndromes reported by Gehi et al described freedom from AF rates of 66% and 37% on and off anti-arrhythmic drugs¹⁹³. A multicentre series in a persistent and long-standing persistent AF population reported 52% of patients arrhythmia free off anti-arrhythmic drugs and 76% with AAD¹⁹⁴. More recently, one year freedom from AF rates of 86% on anti-arrhythmic drugs and 62.2% without has been described¹⁹⁵.

All the hybrid techniques have a higher complication rate than published series of catheter ablation. When grouped together the major complication rate could be as high as 7.4% with a mortality rate of 0.5%¹⁸⁶. The unilateral VATS approach does appear to have a more favourable risk factor profile when compared to the bilateral VATS or sub-xiphoid approach and it may be that both of these

methods have excellent outcome data in the hands of experienced operators but necessitate a steeper learning curve.

1.8 Posterior wall isolation: the “box” lesion set

1.8.1 The left atrial posterior wall

The posterior wall of the left atrium lies anteriorly to the oesophagus and is connected to the four pulmonary veins (right and left superior, right and left inferior). Embryologically the left atrial posterior wall is formed from the developing four pulmonary veins¹⁹⁶. On the epicardial surface an epicardial fat pad is seen which usually lies at the level of the inferior pulmonary veins¹⁹⁷. There is a complex autonomic innervation into the left atrial posterior wall and anatomical studies have shown clusters of ganglionic plexi adjacent to the pulmonary veins in four areas.

While the pulmonary veins have been clearly shown to be the predominant trigger of atrial fibrillation many non-pulmonary vein triggers are described and are targets for ablation. Of these ganglionic plexi, rotors and complex fractionated electrograms can be mapped to the left atrial posterior wall. Also, as previously described, it has been demonstrated that fibro-fatty infiltration of the area plays a role in AF development in animal models. In a 1995 study of canine models AF was induced by rapid atrial pacing and the shortest AF fibrillatory cycle lengths were seen at sites on the LAPW. These were strongly associated with sustained AF and cryoablation at these points resulted in AF termination in 9/11 dogs¹⁹⁸. Subsequent animal studies have reinforced the importance of the LAPW in the development and maintenance of AF^{199,200}. The consistent presence of important rotors on the LAPW has also been demonstrated in humans^{201,202}.

The importance of the left atrial posterior wall in animal models and in the mapping of AF triggers has led to this being a specific target for ablation therapies. The theory behind left atrial posterior wall isolation is that by modifying atrial substrate to isolate this area in conjunction with isolation of the pulmonary veins a number of AF triggers are treated to stop AF development while modification of the posterior wall reduces the substrate that potentiates persistent atrial fibrillation. Isolation of the LAPW is the basis for surgical and hybrid AF ablation.

1.8.2 The Box lesion Pattern via Catheter Ablation

Prior to their landmark work on pulmonary vein isolation Hasseguire et al had attempted fluoroscopic guided catheter ablation for atrial fibrillation in the left atrium based on a surgical lesion set. The development of three-dimensional mapping technology in the late nineties allowed greater spacial information regarding the ablation catheter tip. This facilitated early attempts to isolate the pulmonary veins and left atrial posterior wall with radio-frequency²⁰³. Unfortunately the early 3D mapping techniques were unable to produce intact ablation lines and left atrial posterior wall isolation via catheter ablation was not feasible.

As technologies improved, catheter ablation to isolate the posterior wall became possible and was demonstrated to be feasible in twenty-seven patients with persistent atrial fibrillation by Sanders et al²⁰⁴. They performed standard pulmonary vein isolation with wide antral ablation and then isolated the posterior wall with lines connecting the top of the superior pulmonary veins and the bottom of the inferior PV's. The LAPW was checked for exit block following isolation. Isolation was successful in all patients but with significant additional procedural time (64 +/- 16 mins vs 199 +/-46 mins). Posterior wall isolation terminated atrial fibrillation in 19% of patients. At 21 +/- 5 months of follow-up 63% remained in sinus rhythm. 12 of the 27 patient remained in sinus rhythm off antiarrhythmic

drugs after one procedure while a further 4 patients required a second procedure to isolate the LAPW²⁰⁴.

Lim et al again demonstrated the feasibility of electrical isolation of the pulmonary veins and posterior left atrium but this time via a single continuous ring of radiofrequency lesions in a consecutive series of 100 patients. The cohort of patients were of mixed atrial fibrillation syndromes and two-thirds were paroxysmal. 46 patients had recurrence of either atrial fibrillation or atrial flutter and all patients with recurrence of atrial fibrillation who were re-studied had evidence of LAPW reconnection. Recurrence of other atrial arrhythmias such as left atrial flutter was often seen due to macroreentry involving discontinuity in linear lesions²⁰⁵.

In 2009 Tamborero et al studied 120 patients with atrial fibrillation (two-thirds paroxysmal) brought forward for catheter ablation. They were divided into two matched groups. A lesion set consisting of pulmonary vein isolation, mitral isthmus line and roof line was compared with a group where an additional line connecting the inferior aspect of the two inferior PV's was created to isolate the LAPW. After a mean follow-up of 10 +/- 4 months there was no significant difference in AF recurrence in both groups (40% vs 38%) or left atrial flutter (5% vs 7%). The authors concluded that left atrial posterior wall isolation did not increase the success rate of circumferential pulmonary vein isolation although it is unclear how successful LAPWI was and how complete the lesion set was²⁰⁶.

Several other studies to isolate the LAPW through a single ring to create the box lesion-set have been limited by failure to achieve a complete lesion set or concerns over ablation on the posterior wall and the risk of oesophageal injury. However these have been in mixed groups of patients with predominantly paroxysmal atrial fibrillation and it is perhaps unsurprising that the addition of

posterior left atrial wall isolation adds little to pulmonary vein isolation in paroxysmal atrial fibrillation when outcomes of AF ablation with PVI in PAF are good (table 1-2).

Currently the evidence base for catheter ablation with LAPWI in persistent AF is limited and the outcomes from some of the early studies may be indicative of technological weakness in providing complete posterior wall isolation. Advances in contact force sensing catheters and 3D mapping mean later trials have shown advantages over PVI in persistent AF^{207–209}. Further larger studies are needed but as LAPWI was not one of the STAR AF II lesions the question about its role in persistent AF ablation remains unanswered.

Table 1-2 Summary of trials of LAPW isolation for AF

Trial	Methods	AF syndrome	numbers	Follow-up	Outcome – freedom from atrial arrhythmia		LAPWI confirmed
Sanders ²⁰⁴ 2007	Consecutive series	PsAF + LsPsAF	27	24 months	63%	N/A	all
Kumagai ²¹⁰ 2007	Consecutive series	PAF	91	13 months	90%	N/A	90%
Lim ²⁰⁵ 2008	Consecutive series of patients undergoing LAPWI	PAF, PsAF + LsPsAF	100	12 months	54%	N/A	All 34 patients had redo 88% had gaps in LAPW
Tamorero ²⁰⁶ 2009	PVI + roof line vs LAPWI	PAF, PSAF + LsPsAF	120	10 months	PVI + roof 47% LAPWI – 45%	P = 0.9	Not stated
Yamaguchi ²¹¹ 2010	LAPWI	PAF + PsAF	92	12 months	83%	N/A	100%
Chilukuri ²¹² 2011	LAPWI vs PVI	PAF + PsAF	29	12 months	LAPWI – 25% PVI – 15%	P = 0.44	19%
Lim ²¹³ 2012	LAPWI vs PVI (+MIL in half of each)	PAF, PSAF + LsPsAF	220	24 months	AF free -LAPWI – 74% -PVI – 49% OAT free -LAPWI – 67% -PVI – 64% Arrhythmia free -LAPWI – 52% -PVI – 48%	P = 0.07	109/110 patients

Sohns ²¹⁴ 2014	LAPWI vs PVI	PAF + PsAF	80	12 months	LAPWI – 58% PVI – 57%	ns	100%
Saad ²¹⁵ 2014	Consecutive series	PSAF + LsPsAF	25	16 months	72%	N/A	100%
O’Neil ²¹⁶ 2015	Consecutive series	PsAF (72%) + PAF	100	12 months	75% arrhythmia free 51% off AAD	N/A	100%
Kim ²⁰⁷ 2015	LAPWI vs PVI + Lines	PsAF	120	12 months	LAPWI – 83% PVI – 63%	P=0.02	
Higuchi ²¹⁷ 2016	LAPWI (age <75 vs age ≥75)	PsAF	229	24 months	53% (<75) 48% (≥75)	N/A	76%
Kumar ²¹⁸ 2016	LAPWI via catheter vs LAPWI by hybrid (non-randomised)	PSAF + PAF	57 (30 catheter, 27 hybrid)	12 months	56% of total cohort	ns	23% via catheter 52% via hybrid
Bai ²⁰⁹ 2016	LAPWI vs PVI	PsAF	52 (32 LAPWI, 20 PVI)	36 months	LAPWI -1yr – 65% -2yr – 50% -3yr – 40% PVI -1yr – 20% -2yr – 15% -3yr – 10%	P<0.01	Second procedure at 3 months.
Cutler ²⁰⁸ 2016	PVI vs LAPWI guided by PW scar	PsAF	141	12 months	LAPWI – 80% PVI – 57%	P=0.005	
McIlennan ²¹⁹ 2017	Consecutive series LAPWI +/- adenosine post ablation	PSAF + LsPsAF	161	12 months	52% (65% with adenosine)	N/A	91%

1.9 Comparison of Surgical and Catheter approaches and Lesion sets

1.9.1 Surgical vs Catheter Ablation

Comparisons of surgical and catheter ablation for atrial fibrillation have pointed towards superior outcomes with regard to freedom from atrial fibrillation with surgical ablation but at a cost of increased complications. The FAST study¹⁸², published in 2012, was the first randomised trial to compare surgical and catheter ablation in 123 patients with paroxysmal or persistent AF. Most

patients had undergone an unsuccessful catheter ablation previously and lesion sets varied between both arms. The catheter ablation technique varied between study sites from PVI only to PVI with lines. Bipolar clamps were used for PVI in the surgical group but there was variation in additional lesions and GP excision between centres. Freedom from AF at one year was significantly higher in the surgical group (65.6% vs 36.5%, $p=0.0022$, off AAD and 78.7% vs 42.9%, $P<0.0001$, on AAD) however this came at a cost of complications. The serious adverse event rate during the 12-month study period was 34.4% in the surgical group versus 15.9% in the catheter group ($p=0.027$), which was primarily driven by procedural adverse events, 23% vs 3.2% ($p=0.001$). Surgical procedural complications included 6 pneumothoraces, one haemothorax and two pacemaker implants.

A meta-analysis of minimally invasive surgery versus catheter ablation in 2016 by Phan et al indicated improved freedom from AF with surgical ablation but increased procedural complications driven by pleural effusions and pneumothorax²²⁰. More recently the CASA AF study in longstanding persistent AF has shown similar findings²²¹. A further study with implantable loop recorder follow-up is ongoing²²² and will be important as outcomes in these patients with catheter ablation alone are poor.

1.9.2 Hybrid vs Catheter AF ablation

A combined sub-xiphisternal epicardial ablation using the *Ncontact* System (Atricure Inc) has been compared to catheter ablation alone in paroxysmal, Persistent and longstanding persistent AF patients. Freedom from AF was greater in the hybrid group compared to PVI alone but in a study of longstanding persistent AF no difference was seen between hybrid ablation and extensive left atrial endocardial ablation. In both studies pre-procedural complications were greater in the hybrid groups^{223,224}. A retrospective study of the technique in persistent AF by Kress et al also reported similar outcomes²²⁵. A randomised prospective study of a two-stage hybrid approach and catheter ablation only has not been performed.

1.10 Thesis Outline

1.10.1 Hypothesis

The optimal ablation treatment of persistent atrial fibrillation (AF) remains unclear and the optimal technique of surgical (epicardial), catheter (endocardial) or hybrid (both) ablation is yet to be established. The initial experience with hybrid AF ablation involving PVI and left atrial posterior wall isolation has shown promising results with regard to freedom from AF. Newer surgical techniques have recently become available that enable isolation of the posterior wall with the so-called 'box lesion-set'⁶. The box-lesion set has shown promise in previous studies with failure related to the technical difficulty in making a complete lesion set^{7, 8,9}.

Recent advances in both surgical and catheter ablation techniques are hypothesized to improve the success rate of ablation by increasing the likelihood of complete posterior left atrial isolation via a box-lesion set. This MD will involve work contributing to and informing the development of a head-to-head trial of surgical and catheter ablation of AF and answer mechanistic questions about left atrial ablation.

I aim to study hybrid and catheter ablation techniques for posterior wall isolation addressing the following questions:

- **Does Posterior Left Atrial Wall Isolation in patients with persistent atrial fibrillation provide longstanding freedom from Atrial Fibrillation?**
- **Can non-invasive assessment of posterior wall isolation be used to predict the success of surgical and catheter ablation for atrial fibrillation?**

- **Does Epicardial ablation provide lasting modification of the cardiac autonomic nervous system?**
- **Can the development of new catheter technologies confer greater stability and contact in left atrial ablation?**

These 4 projects will answer questions that will allow us to design a further trial (not part of this MD but following from the work in this MD thesis) that will be a randomised comparison of Left Atrial Posterior Wall isolation by hybrid ablation versus catheter ablation only.

The four projects need to be completed before this trial can be designed as they will provide data necessary for:

- 1) Performing power calculations on projected outcome measures,
- 2) Planning clinical stages in the patient pathway in the trial (such as non-invasive assessment of posterior wall isolation following the surgical procedure, but prior to second stage catheter ablation),
- 3) Understanding the relative contribution of targeted ganglionic plexi ablation versus electrical isolation in achieving successful therapy, and
- 4) Which catheter apparatus is likely to give the best results in the catheter ablation only approach?

2 Chapter 2 - Catheter Ablation of Atrial Fibrillation with Left Atrial Posterior Wall Isolation at Derriford Hospital, Plymouth.

2.1 Abstract

Aims: To determine the acute success rate and long-term freedom from atrial fibrillation in patients who undergo catheter ablation for atrial fibrillation with the lesion set of left atrial posterior wall isolation.

Methods: This was a partially retrospective study of patients who had undergone left atrial posterior wall (LAPW) isolation via catheter for symptomatic persistent atrial fibrillation or recurrent AF following pulmonary vein isolation. Procedural success and complications were recorded either retrospectively from patients notes or prospectively at the time of procedure. Successful LAPW isolation was documented as were procedural complications. Follow-up was via telephone or face-to-face clinics at 4 months 12 months and 24 months post procedure. 7-day holter monitoring was performed at 12 months and 24 months.

Results: Thirty-three patients (29M, 4F) underwent LAPWI. 25 had PsAF and 8 PAF. LAPWI was successful in 70% (23/33). The single procedural complication was tamponade requiring pericardiocentesis.

After a median of 24 months follow-up (IQR 16-24) 20 patients were free from arrhythmia recurrence (60%). 19 (58%) off antiarrhythmic drugs. Having a complete lesion set with confirmed LAPW isolation was associated with better outcomes. 17/23 (74%) remained free of atrial arrhythmia compared to 3/10 (30%) where LAPW isolation was not seen ($p=0.026$) and median arrhythmia free duration was 24 months (16-24) vs 12 months (11-15) respectively ($p=0.017$).

Conclusions: Left atrial posterior wall isolation is feasible with a limited complication rate. Outcomes are significantly improved where successful left atrial posterior wall isolation is confirmed with entrance and exit block. When the lesion set is complete freedom from atrial arrhythmia appears superior to other lesion sets but randomised comparison in larger trials are needed.

2.2 Aims

To determine the acute success rate and long-term freedom from atrial fibrillation in patients who undergo catheter ablation for atrial fibrillation with the lesion set of left atrial posterior wall isolation.

2.3 Background

Left atrial posterior wall isolation and its development as a technique in the ablation of atrial fibrillation is described at length in Chapter 1. The technique has been used as a treatment for atrial fibrillation at Derriford Hospital for over 10 years. The lesion pattern was initially used surgically in HIFU ablations but shortly after that catheter technologies were utilised to create the same lesion set. This was decided on following the initial promising studies described in chapter 1 with the aim of improving outcomes from ablation in persistent AF.

In the first catheter ablation cases the lesions were created with the Ablation Frontiers PVAC/TVAC system (*Medtronic Inc, Minneapolis, USA*) however rigorous testing for electrical isolation proved difficult. It wasn't until 3D mapping systems were adopted for the lesion pattern that electrical isolation for the posterior left atrium could be confidently predicted. This chapter relates to those who underwent 3D mapping only.

2.4 Methods

Patients with symptomatic persistent atrial fibrillation refractory to anti-arrhythmic medications referred to the electrophysiological service at Derriford Hospital Plymouth are considered for catheter ablation. Those with continuous AF durations of less than 12 months who do not have severely enlarged left atria are offered catheter ablation with pulmonary vein isolation plus left atrial

posterior wall isolation. Patients with unfavourable characteristics for catheter ablation may be considered for a two-stage hybrid AF ablation (chapter 3). Left atrial posterior wall isolation via catheter ablation is also considered for those patients who have had recurrent symptomatic atrial fibrillation following previous ablations.

In this partially retrospective observation study of clinical practice we looked at all patients who had undergone left atrial posterior wall isolation via catheter between 2012 and the end of 2016. For the patients who had previously undergone the procedure baseline demographics and ablation details were obtained from the medical notes with 7-day ambulatory monitoring obtained from the medical notes or offered again if patients had not undergone sufficient follow-up.

Patients from 2014 were followed-up prospectively with demographic and ablation details documented at the time of procedure. Standard follow-up was then with ECG's and clinical follow-up at four, twelve and twenty-four months. Seven-day ambulatory loop monitoring was performed at 12 and 24 months with further clinical review guided by individual patients symptoms.

As this was an audit of standard clinical practice formal ethical approval was not sought.

2.4.1 Catheter Ablation

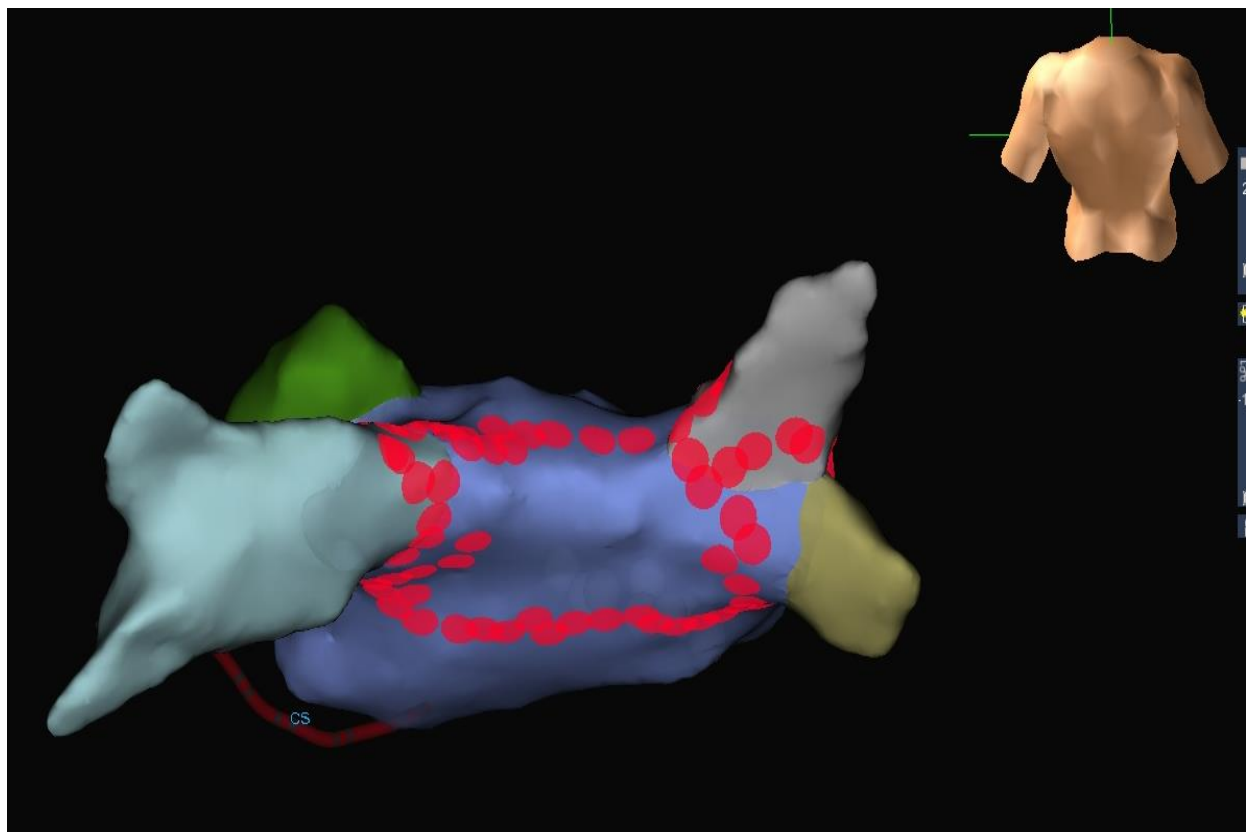
All catheter ablation patients undergo radio-frequency ablation under general anaesthesia. Access is via the right femoral vein and right subclavian or internal jugular vein with placement of decapolar catheters in the coronary sinus and the right atrium.

Atrial trans-septal puncture is performed under fluoroscopic guidance using standard orthogonal views and unfractionated heparin is given to maintain an activated coagulation time of greater than

300s. SL1 and Agilis sheaths (St Jude Medical, St. Paul, Minnesota, USA) are passed through the same aperture in the interatrial septum to give access to the left atrial chamber. If the patient is in atrial fibrillation, we cardiovert to sinus rhythm as we have found voltage mapping to be inconsistent in atrial fibrillation; sinus or paced rhythm permits propagation mapping. Mapping and ablation is performed using the Velocity/Precision system (*St Jude Medical* St. Paul, Minnesota, USA) and the Tacticath Quartz (St Jude Medical, St. Paul, Minnesota, USA) contact force sensing catheter. Three early patients in this series underwent mapping and ablation using the CARTO system (*Biosense Webster*, Diamond Bar, California, USA).

A three-dimensional voltage map of the left atrium is created using the St Jude Velocity/Precision system and an AFOCUS II catheter (St Jude Medical, St. Paul, Minnesota, USA). Standard settings are between 0.1 mV and 0.13 mV (grey colour scale) to 0.5 mV (purple colour scale) with healthy tissue identified by areas of higher voltage and areas of low electrical amplitude indicating scar..

Pulmonary vein isolation is performed first by encircling the two pairs of veins using 25 Watts on the left atrial posterior wall with a 15 second maximum duration at any one site and 30-35 Watts elsewhere aiming for LSI of 5.5 to 6.0. After confirmation of pulmonary vein isolation with entry and exit block, two lines of closely placed point-by-point lesions were then performed. The first linking the antero-superior margins of the two regions to form the roof line and the second, a curved line of lesions from the inferior margin of the left inferior pulmonary vein to the inferior margin of the right inferior pulmonary vein across the floor of the left atrium, curving away from the posterior wall, to form the floor line.

Figure 2-1 Left atrial posterior wall isolation (ablation lines shown by red dots)

Left atrial posterior wall isolation is confirmed by entrance and exit block into and out of the left atrial posterior wall and by demonstration of pacing and capture within the isolated area without conduction to the rest of the atria. Evidence of block is re-checked following adenosine administration sufficient to provoke transient complete heart block. If the veins and posterior wall of the left atrium remain isolated, no further ablation is required.

Figure 2-2 Confirmation of Left atrial posterior wall exit block. Pacing above the resting heart rate on the Tacticath ablation catheter inside the LAPW fails to capture the rest of the atrium which is beating independently. Capture within the posterior wall is seen on the A-FOCUS II mapping catheter



Post procedure, all patients are prescribed one month of proton-pump inhibitors as part of the oesophageal protection protocol.

2.4.2 Follow-up

Patients who were included in the study prospectively were offered telephone follow-up with a standard ECG at 4 months and face-to-face follow-up with seven-day holter monitors at 12 and 24 months. Further follow-up and monitoring was driven by symptoms.

For the retrospective patient's notes, previous letters and redo procedures were looked at to

document any recurrence of symptoms or documented atrial arrhythmia. Patients were telephoned for symptom assessment at 12 months and 24 months with seven-day holter monitoring at the same time. If the procedure was greater than 24 months prior to the start of the trial the patients had a telephone assessment of symptoms and a single seven-day monitor.

We aimed to report on the acute success of left atrial posterior wall ablation, time to atrial arrhythmia recurrence and any complications.

2.5 Results

Between October 2012 and November 2016 thirty-three patients underwent left atrial posterior wall isolation. The baseline characteristics are listed in the table below.

Table 2-1 Summary of baseline characteristics of patients undergoing LAPW isolation for AF

Baseline Characteristics	Median value (Interquartile Range)
Age	62.5 (52.75-70)
Sex	29 Male, 4 Female
LA AP Diameter	40mm (35-45)
Ejection Fraction	55% (50-55)
CHADsVASc Score	1 (0-1)
Continuous AF duration	8 months (2-12)
Previous Ablation	20/33 (61%)
AF Syndrome	PAF 8 (24%), PsAF 25 (76%)

Twenty-five of the thirty-three patients had persistent atrial fibrillation and twenty of the procedures were redo ablations. Following the ablation procedure the posterior wall was isolated with confirmed entrance and exit block in twenty-three patients (70%). All patients were discharged in sinus rhythm. After a median of 24 months follow-up (IQR 16-24) 20 patients were free from arrhythmia recurrence (60%). 19 (58%) off antiarrhythmic drugs.

Better outcomes from ablation were associated with successful left atrial posterior wall isolation. In the group who had the LAPW successfully isolated with confirmed entrance and exit block at the end of the ablation 17/23 (74%) remained free of atrial arrhythmia compared to 3/10 (30%) in whom entrance and exit block from the LAPW was not seen ($p=0.026$). Freedom from atrial arrhythmia was also significantly longer in the twenty-three patients with confirmed LAPW isolation at the end of the ablation compared to those in whom LAPW isolation was not possible; 24 months (16-24) vs 12 months (11-15) respectively ($p=0.017$).

There were twenty-five patients with persistent atrial fibrillation who underwent LAPWI and, of these, isolation was confirmed following ablation in 19 (76%). Sixteen of twenty-five (64%) were free of atrial arrhythmia at the end of the follow-up period.

Of the eight patients with paroxysmal atrial fibrillation only 4/8 patients (50%) had successful left atrial posterior wall isolation. Recurrence of AF occurred in 4/8 patients (50%), 3 of who had unsuccessful LAPWI.

Successful left atrial posterior wall isolation was numerically fewer in the 20 patients who had undergone previous AF ablation than those who had not; 13/20 (65%) vs 10/13 (77%) although this

was not statistically significant ($p=0.472$). There was no significant difference in freedom from atrial arrhythmia 13/20 (65%) vs 7/13 (54%) ($p=0.543$).

2.5.1 Complications

One complication of a tamponade requiring pericardiocentesis occurred following the ablation procedures. No other complications were seen, and no oesophageal complications were noted per-procedurally or during the follow-up period.

2.6 Discussion

In this single centre series of left atrial posterior wall isolation for the treatment of atrial fibrillation the two-year freedom from atrial arrhythmia was 60%. The procedure appears to be safe with only one complication seen in this cohort of patients. Of those patients with persistent atrial fibrillation, freedom from atrial arrhythmia was 64% and this is favourable compared to the STAR AF II lesions¹³⁸ where the addition of linear or CFAE ablation did not improve outcomes compared to pulmonary vein isolation alone. It is important to note that left atrial posterior wall isolation was not included as a lesion set in STAR AF II.

The benefit of LAPWI over PVI in previous studies is variable with no statistically significant difference seen in studies on mixed groups of AF patients by Tamborero²⁰⁶, Chilukuri²¹², Lim²¹³ and Sohns²¹⁴. In more recent studies in persistent AF patients Bai²⁰⁹, Cutler²⁰⁸ and Kim²⁰⁷ have reported improved outcomes of the lesion pattern compared to pulmonary vein isolation alone. It is possible that in these later studies technological improvements in AF ablation equipment such as mapping software and contact force catheters may have resulted in better outcomes.

In this series successful left atrial posterior wall isolation with confirmed entrance and exit block at the end of the ablation procedure made a significant difference to outcomes. It has previously been shown in surgical AF series of LAPWI that enduring posterior wall isolation is associated with improved outcomes²²⁶. The rate of confirmed LAPWI in the series is in keeping with other published studies where rates of confirmed LAPWI vary from between 19-100%^{211,212}. The wide variability in quoted LAPWI outcomes is likely a reflection of ablation technology and the rigor of testing for entrance and exit block into and out of the LAPW. In many of these studies it is unclear as to how this was confirmed and in some studies rates are not quoted. In the largest study of this lesion pattern using modern ablation technology by Higuchi et al, 229 patients were enrolled and successful LAPWI was achieved in 76%²¹⁷. This is equivalent to the rate of successful LAPWI in this series.

Confirmed left atrial posterior wall isolation is clearly an important factor determining outcomes and the administration of adenosine has been shown to highlight reconnections. McIlennan et al have demonstrated that adenosine administration can unmask connections into the LAPW in 17% of cases and improve single procedure success²¹⁹. Reconnections into the LAPW are likely to influence outcomes and arrhythmia recurrences. Bai et al repeated the electrophysiological study in all patients who had undergone LAPWI at three months. In the first ablation procedure all 32 patients achieved LAPWI but at the repeat study only 20 (63%) had an intact lesion set²⁰⁹. Reconnections into the pulmonary veins is an obstacle to long term success of PVI and routine re-study and ablation of re-connections improves outcomes in paroxysmal atrial fibrillation^{227,228}. Given the difficulty of achieving confirmed LAPWI future study protocols could mandate a second electrophysiological study and ablation after the three-month blanking period thereby maximising the chances of achieving a durable lesion pattern and gaining maximum benefit for it.

2.6.1 Limitations

This study was a mixed retrospective and prospective audit of clinical practice in a mixed cohort of atrial fibrillation patients. Both persistent and paroxysmal atrial fibrillation patients were included and many patients had undergone previous ablations. It is therefore not possible to draw conclusions about the benefit of the lesion set in paroxysmal or persistent AF or to compare against alternative ablation approaches. As a database of consecutive cases inherent biases may exist in patient selection and choice of ablation approach.

Data collection was also limited to that which was available in the medical notes or on hospital computer systems. While we aimed for ECG's and ambulatory monitoring at the pre-specified time points this was not always performed in the retrospective cases due to non-attendance and in this case the outcomes were determined by telephone calls and ECG's. Even with follow-up limited to 4, 12 and 24 months arrhythmia recurrences may have been missed although it is likely that symptomatic arrhythmia recurrence would have been apparent in the medical notes.

I was unable to do any detailed study of the raw velocity data and draw any conclusions from the 3D maps and propagation maps that were generated due to a large data loss. This meant I could only rely on procedure reports, letters and notes for the results. Had this information been available a number of questions could have been addressed regarding scar mapping and outcomes. These include: why LAPWI was more difficult in the redo PAF group than the PsAF group? What role did the LAPW play in these patients and what technical factors prevented an intact lesion set?

2.7 Conclusions

Left atrial posterior wall isolation is feasible in the majority of cases with a low complication rate.

Outcomes are significantly improved where successful left atrial posterior wall isolation is confirmed with entrance and exit block. In persistent atrial fibrillation freedom from atrial arrhythmia appears superior to the STAR AF lesion sets when left atrial posterior wall isolation is confirmed with entrance and exit block. Randomised comparisons in larger trials are needed.

3 Chapter 3- Hybrid Atrial Fibrillation Ablation for persistent Atrial Fibrillation

3.1 Abstract

Background: Treatment of long-standing persistent Atrial Fibrillation (LsPsAF) remains challenging, with catheter ablation outcomes inferior to those for paroxysmal atrial fibrillation, and the optimal ablative approach is unclear. European guidelines suggest a role for Hybrid AF ablation. We describe the medium-term follow-up of patients undergoing non-concomitant hybrid AF ablation.

Methods: Patients with LsPsAF (continuous AF duration greater than one year) are offered non-concomitant hybrid ablation to isolate the Left Atrial Posterior Wall (LAPW) following an AF Heart team discussion. Patients first undergo unilateral video assisted thoracoscopic (VATS) epicardial ablation with subsequent electrophysiological study (EPS) and ablation to complete LAPW isolation and add a cavo-tricuspid isthmus ablation after a minimum of two months. Follow-up is via clinical review at 4, 12 and 24 months with 7-day ambulatory ECG monitoring at 12 and 24 months.

Results: 57 patients with symptomatic LsPsAF have undergone the VATS procedure; two were abandoned due to pericardial adhesions. Conversion to open thoracotomy was necessary in two patients and one patient had a fatal CVA 24 hours post-operatively. Forty-nine patients have undergone both stages and 40 are post the blanking period with a median follow-up of 20 months (IQR 12-25.5). 57% of these are free of any atrial arrhythmia recurrence off anti-arrhythmic drugs. There has been a significant reduction in arrhythmia burden; currently 82.5% are in sinus rhythm (70% off AAD).

Of those with over 1 year of follow up, 87.5% are currently in sinus rhythm.

Conclusions: Following 2 stage non-concomitant hybrid ablation, 57 percent of LSPsAF patients are free of arrhythmia recurrence off anti-arrhythmic drugs . 82.5% are currently in SR (70% off AAD). This is superior to published outcomes of catheter ablation in LSPsAF. Care is required to avoid right phrenic nerve injury. Further study is required to determine long-term outcomes and to compare with alternative techniques.

3.2 Background

Treatment of atrial fibrillation (AF) via catheter ablation has consistently been shown to be superior to treatment with anti-arrhythmic medication alone and this is reflected in contemporary guidelines^{229,230}. Outcomes for persistent AF ablation are inferior to those in PAF²³¹ and are not improved by the addition of roof and mitral isthmus lines or the targeting of complex fractionated electrograms (CFAE)¹³⁸. Outcomes for patients with long-standing persistent atrial fibrillation (continuous AF duration of greater the 12 months) are even worse²³².

Surgical treatment for AF has been available for almost 25 years in the form of the Cox-MAZE procedure. Yet despite good outcome data¹⁷⁴ from the procedure, its complexity has limited widespread use¹⁸⁵. Surgical AF ablation has been revived by the development of minimally invasive techniques either as standalone procedures or as part of hybrid ablation in combination with catheter ablation. Initial non-randomised published data in mixed AF populations reported variable success rates of between 37%-90% freedom from AF at one year for all AF types and 28-80% free from AF in those with persistent atrial fibrillation^{191,192}. Recently surgical and hybrid ablation techniques have been given a IIa recommendation in the latest ESC guidelines for the management of atrial fibrillation²²⁹.

We describe our single centre experience of non-concomitant staged hybrid ablation for long-standing persistent atrial fibrillation.

3.3 Methods

3.3.1 The Hybrid Atrial Fibrillation Pathway and AF Heart team

All symptomatic patients with persistent atrial fibrillation and characteristics unfavourable for standard catheter ablation alone (such as continuous AF duration of longer than one year, increased BMI, enlarged left atrium or previous failed catheter ablations) are referred to the AF heart team to be considered for hybrid AF ablation (surgical VATS procedure followed by catheter ablation after greater than two months). Each case is discussed individually with review of symptoms, cardiac investigations (including cardiac CT and/or invasive angiography) and co-morbidities. An individual strategy for each patient is formulated that may include offering catheter ablation, hybrid ablation or medical management with rate control only.

Those suitable for hybrid ablation are reviewed in a cardiac surgery clinic before being listed for the first stage procedure. Patients are informed that in situations where there is left atrial appendage thrombus or significant pericardial adhesions the procedure may be converted to an open sternotomy if required.

3.3.2 The surgical 1st stage

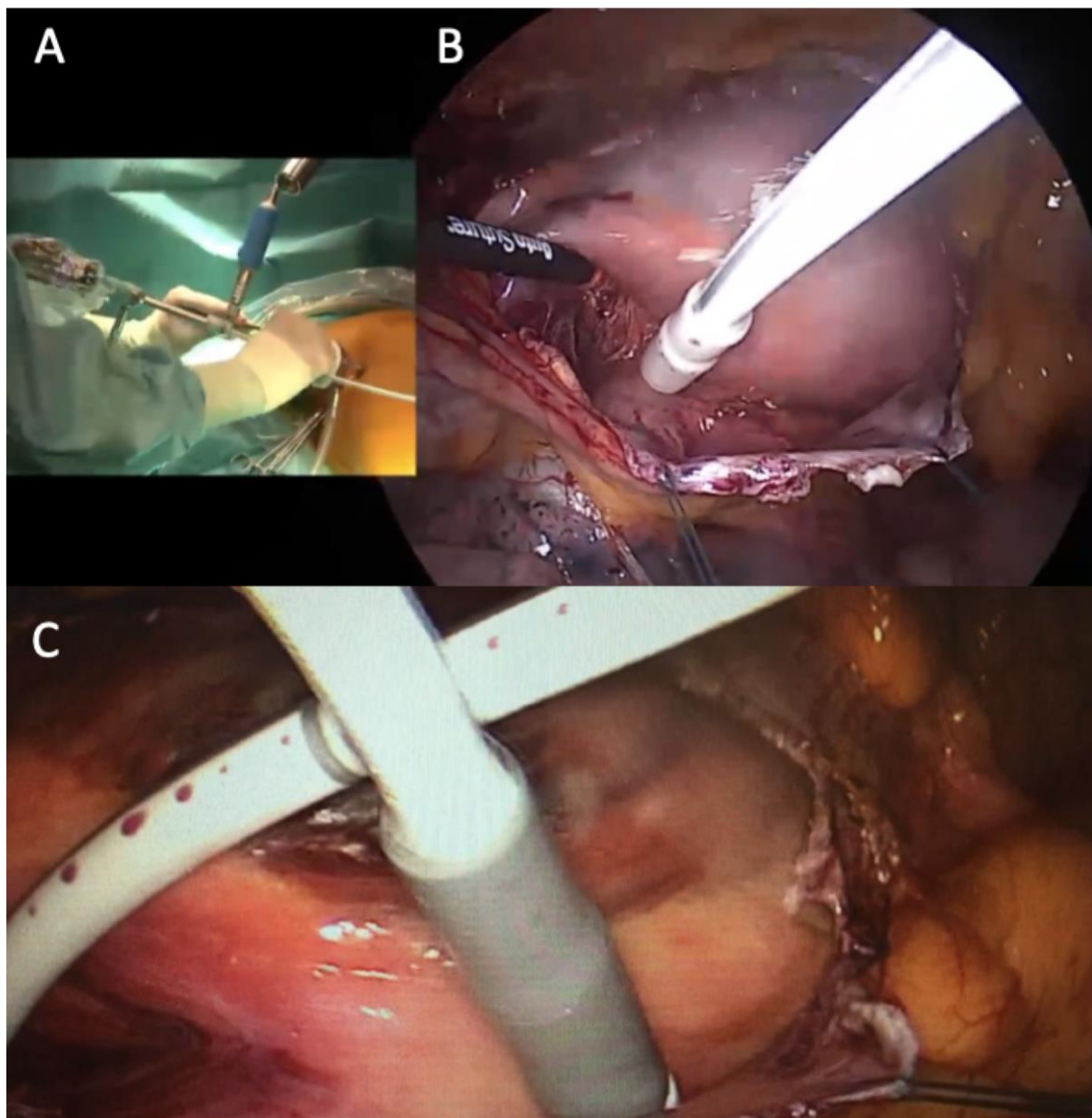
All patients have CT coronary angiography preoperatively to assess their cardiac anatomy and eliminate coronary artery disease. Patients undergo surgery partially anticoagulated (INR \approx 1.8) or after 48 hours off DOAC (Direct Oral Anti-coagulant). Following induction of anaesthesia, pre-procedural transoesophageal echocardiogram is undertaken to exclude left atrial appendage thrombus.

The operative procedure for monolateral thoroscopic AF ablation is described in detail in the literature by Bisleri and Muneretto²³³. The patient is placed in a supine position and the patient is draped in traditional fashion as if for a bilateral thoroscopic procedure. The third, fourth and fifth intracostal spaces of the right thorax are marked for port positioning. The camera port is positioned at the level of the fourth intercostal space on the anterior axillary line whereas the other ports are

positioned slightly more anteriorly in the third and fifth intercostal spaces. Once marked the patient is positioned 30 degrees towards the left decubitus, the right lung is deflated and the three 10mm ports are placed.

The pericardium is opened longitudinally 1 to 2 cm above the phrenic nerve and a wide dissection of the transverse sinus is performed using an endopecanut blunt dissector. A pericardial reflection between the inferior vena cava and right inferior pulmonary vein of the oblique sinus is then created. Suction assisted, mono and bi-polar epicardial ablation is performed after removal of epicardial fat and administration of heparin to produce a box lesion isolating the posterior left atrium and the four pulmonary veins. The autonomic ganglia on the right are ablated or excised following high frequency stimulation to identify sites of vagal response.

Figure 3-1. Panel A – Ports are introduced in the right thorax. Panel B – The pericardium is dissected and the Cobra Fusion Ablation device is introduced. Panel C – The Cobra Fusion is passed around the pulmonary veins to encircle the left atrial posterior wall



With experience the surgical ablation technique has evolved at Derriford. Initially three, but now up to eight cycles of mono and bipolar radiofrequency ablation are performed following an increasingly aggressive removal of epicardial fat. The temperature-controlled Fusion ablation system (cycling up to 150W to deliver 70°C to tissue) and the presence or absence of left atrial posterior wall conduction block following the ablation (documented by intra-operative pacing within the isolation zone post DCCV) determine the number of cycles of ablation.

Patients go to the ward and are started on a DOAC (Dabigatran) on the evening of the surgery. The patients are mobilised the day after surgery and usual discharge is 48 hours postoperatively.

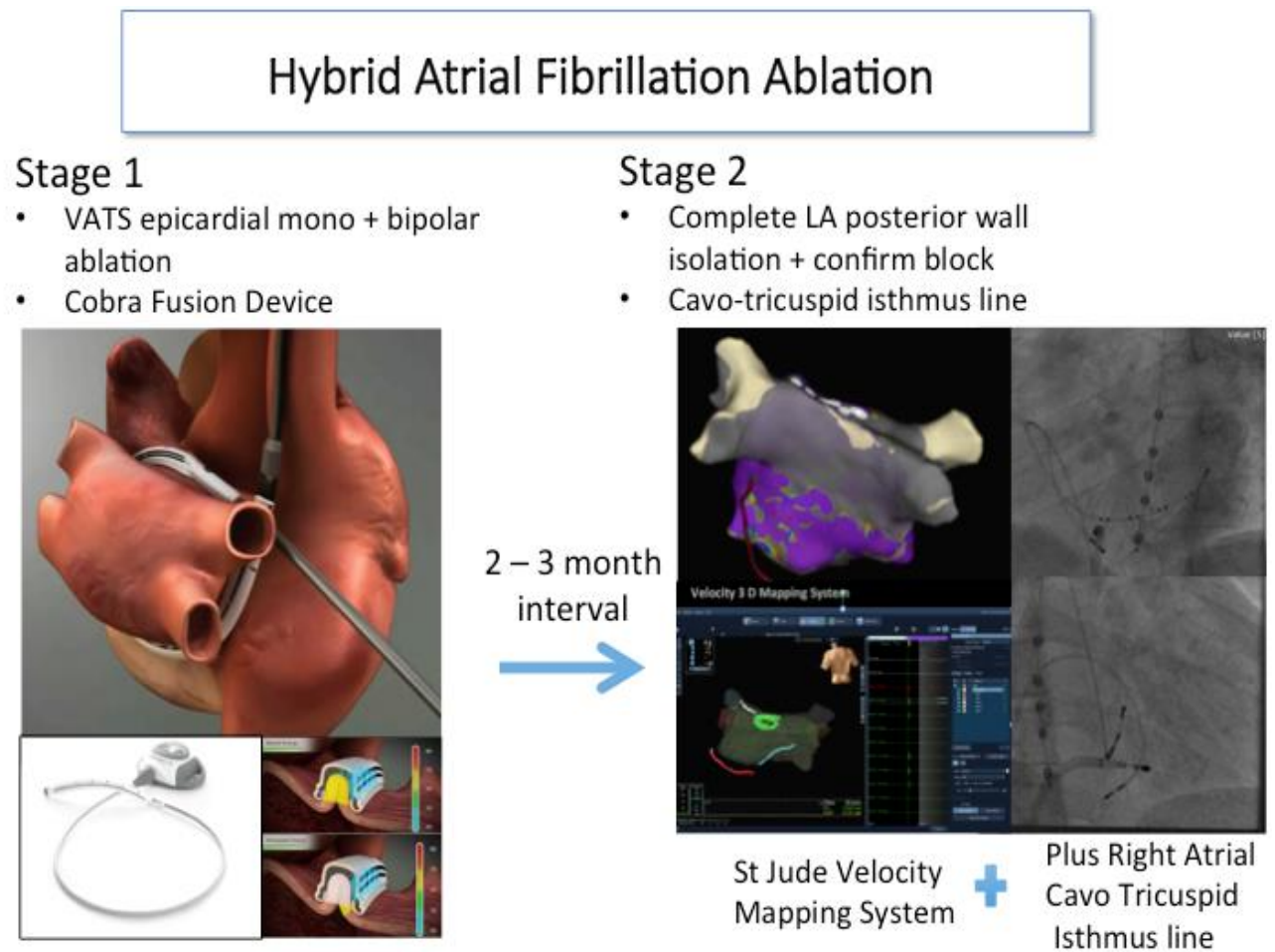
3.3.3 The electrophysiological second stage

The second stage procedure is performed a minimum of 8 weeks following the epicardial surgical ablation to allow time for conduction to recover at any non-permanent sections of the surgical ablation line. Until now anticoagulation has been discontinued 36 hours prior to the procedure if patients are on a DOAC, or, if on Warfarin, the procedure is performed with the drug uninterrupted and an INR of 2.0-2.5. The study is performed under a general anaesthetic via vascular access from the right femoral ± right subclavian/internal jugular veins. The technique for electrophysiological study and left atrial posterior wall isolation has been described in Chapter 2. In addition to LAPWI a cavo-tricuspid isthmus line is performed in all patients.

If the 'box' lesion created by the Cobra Fusion device is not electrically intact, further ablation is performed, guided by the initial voltage map and propagation maps. Gaps identified in the ablation lines are closed by irrigated radiofrequency ablation lesions delivered with a Tacticath Quartz (St Jude Medical, St. Paul, Minnesota, USA) contact force sensing catheter achieving target levels of minimal contact force (greater than 1g above baseline and mean force greater than 10g), optimal stability and force-time integral appropriate for the lesion position. Precise identification of the position of residual electrical connection across the surgical line of block is achieved by placing the AFOCUS II mapping catheter against the left atrial posterior wall, close to areas identified as defective, and using the earliest electrical signals seen at a particular pole of the mapping catheter to guide RF lesion delivery. Propagation mapping in sinus rhythm is also used to identify areas of breakthrough in the surgical lines. Ablation is delivered with 25 Watts on the left atrial posterior wall

and 30-35 Watts elsewhere. Adenosine is administered and lines of block are re-checked at the end of the case.

Figure 3-2 The non-concomitant Hybrid Ablation process involves an initial surgical epicardial ablation with a staged second catheter ablation study.



Rarely, an atypical atrial flutter persists after left atrial posterior wall isolation. Propagation mapping may indicate the need for additional linear ablation such as a mitral isthmus line to terminate the flutter. A mitral isthmus line is not part of our standard lesion set.

All patients are prescribed one month of proton-pump inhibitors as part of the oesophageal protection protocol post-procedure.

3.3.4 Follow-up

Patients who undergo hybrid ablation for atrial fibrillation are followed-up at four months; one year and two years post the electrophysiological second stage. This includes an assessment of symptoms and resting ECG at four months, 12 months and two years with seven-day ambulatory monitoring at one and two years. Patients are asked to undertake ECG documentation at the time of any symptoms outside these times and to send in the ECGs obtained.

In this study, we report time to first documented episode of atrial arrhythmia, defined as lasting at least 30 seconds on monitoring, following the 3-month blanking period after the second stage electrophysiology procedure and the prevalence of sinus rhythm at time of analysis and for patients over one year following both stages.

3.4 Results

Ninety patients entered the pathway between 2013 and mid 2017. Of these, sixty-four were deemed suitable for hybrid ablation following MDT discussion and clinic review. Fifty-seven patients have undergone a VATS procedure. Two patients had extensive pericardial adhesions so the procedure was abandoned, these patients had not consented to sternotomy. In two further patients, the surgery was converted to planned sternotomy. This was to facilitate pericardial access due to lung adhesions in one case and to allow for left atrial appendage occlusion due to presence of left atrial appendage thrombus identified on transoesophageal echocardiography in the other. One patient had a fatal CVA 24 hours post op. Fifty-four patients have so far been referred on for the second stage (patient characteristics are shown in Table 3.1) and 49 patients have undergone second stage, a median of 156 days post-surgery. The results and outcome data in this paper refer to the cohort

who have completed both stages. All statistical analysis is performed using 'R' version 3.2.2 (C. 2015. The R Foundation for Statistical Computing)

Table 3-1 Summary of demographics and clinical characteristics of patients undergoing Hybrid ablation

Clinical Characteristics	Continuous variables median (IQR)
Age (years)	67.5 (60 -70.75)
Sex	44 M, 10 F
BMI	30 (27.6 -32)
Continuous AF Duration leading up to ablation (months)	24 (13.25-35.75)
Time in AF over previous 10 years (months)	34.5 (24-45.25)
Number of DCCV	2 (1-2.75)
CHADS-VaSc Score	2 (1-2)
Left Atrial AP diameter (mm)	46 (43-49)
Left Ventricular Ejection Fraction (%)	55 (50-59.75)
EHRA symptom class	2 (2-2)

3.4.1 First stage surgical ablation

The median procedure duration including anaesthesia was 180 minutes and following ablation, epicardial left atrial conduction block was demonstrable in thirty of the fifty-four (55.5%) and 27 of the 49 (55%) who have undergone subsequent EPS. Patients were discharged a median of 3 days (IQR: 3-4) post operatively and 22 of the 54 (40.7%) were discharged in sinus rhythm after the first stage of the procedure.

On presentation for the second stage EP study seventeen out of forty-nine patients (35%) were in sinus rhythm, eight patients presented in an atypical atrial flutter (16%), one in an atrial tachycardia (2%) and the rest were in atrial fibrillation (47%).

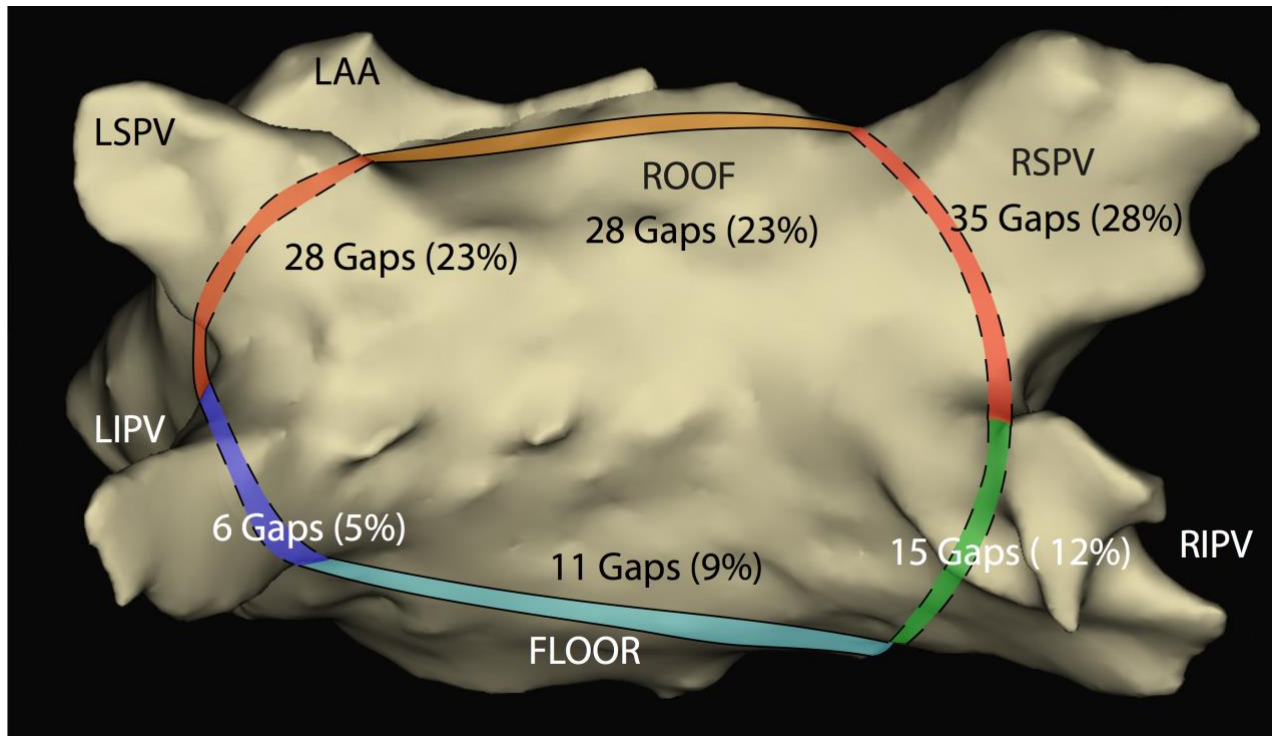
3.4.2 Second stage electrophysiological study

Electrophysiological study was performed in all forty-nine patients without complication. The LA posterior wall was isolated at baseline in ten patients (20.5%) and further LA ablation was required in thirty-nine (79.6%). Of the twenty-seven patients with confirmed epicardial LA posterior wall isolation following surgical ablation, only eight remained isolated at the electrophysiological study second stage (29.6%). LA posterior wall isolation was achieved in all but two patients (4%). A Cavo-tricuspid isthmus line was completed in all but five patients, due to operational time constraints.

3.4.3 Gaps in the Epicardial Ablation lines

Gaps in the surgical 'box' were identified most commonly along the left superior pulmonary vein, roofline and around the right superior pulmonary vein. In our series, there was a median number of 3 gaps (IQR: 1-4) per patient (figure 3-2).

Figure 3-3 Location of gaps in epicardial ablation lines requiring further ablation to complete left atrial posterior wall isolation at the second catheter ablation stage. Sites of gaps in the epicardial ablation lines that were identified at the electrophysiological second stage procedure. Gaps in the ablation lines were most commonly seen in the roof lines



3.4.4 Follow-up

Forty-nine patients have undergone both stages. Of them, forty-three are currently more than three months after the catheter second stage. At the time of submission, 43 patients have a median follow-up of 19 months (IQR: 11.5 - 25) and twenty-seven (62.7%) remain arrhythmia free – twenty-six (60.4%) off anti arrhythmic drugs. Sixteen patients had a recurrence of an atrial arrhythmia outside of the three-month blanking period. At most recent follow-up, thirty-six of the 43 patients (83.7%) are in sinus rhythm, thirty-one (72%) off antiarrhythmic drugs. One patient had recurrence of AF early in the blanking period after the 2nd stage procedure but refused further rhythm control management so is included as a failure in these results.

Thirty-two patients are more than 12 months (median 22.5, IQR 17.75 – 32.25 months) post the second catheter ablation stage. Of these, nineteen (59.4%) have remained arrhythmia free off antiarrhythmic drugs following the three-month blanking period after the catheter second stage. Twenty-eight of this group of patients are currently in sinus rhythm (87.5%) and twenty-three of these (82%) are off antiarrhythmic drugs.

Table 3-2 Summary of arrhythmia recurrences

Recurrences		
Recurrence Rhythm	Management	Current Rhythm
AF	DC Cardioversion	Persistent AF
		Persistent AF
		Persistent AF
	Extensive anterior LA scar	Permanent AF
	Refused further rhythm management	Permanent AF
	Early reconnections so further LA ablation	SR off AADs
	Self-reverted	SR off AADs
	Chemical CV	SR on Amiodarone
	DCCV	SR off AADs
	DCCV	SR off AADs
	Amiodarone augmented DCCV	SR on Amiodarone
	Chemical CV	SR off AADs
Atypical AFL	EPS with intact box lesion but extensive LA scar	SR on Amiodarone
	Further LA ablation and PPM implantation	Permanent AF
	EPS + ablation	Atypical Flutter
Right Sided AT	RA ablation and PPM implantation for Sinus Brady	SR

3.4.4.1 *Symptom Level*

The European Heart Rhythm Association AF symptom score was recorded at each follow-up visit and the median EHRA symptom score reduced from 2 to 1 following both hybrid ablation stages.

3.4.5 *Complications*

3.4.5.1 *Surgical First Stage*

Two procedures had to be abandoned due to pericardial adhesions prohibiting pericardial access and deployment of the device. Thirteen patients had raised hemi-diaphragm on chest X-ray post-surgical 1st stage. Of these, seven had complete resolution on chest X-ray and fluoroscopy at the electrophysiological 2nd stage; six had continued weakness of right diaphragm with evidence of a residual right phrenic nerve praxis. This resolved in all patients within 12 months. One additional patient developed a right-sided haemothorax after flying within one week of the VATS procedure and a further patient developed a reactive right sided pleural effusion one month after the procedure, both required drainage. One patient with an abnormally high right diaphragm was deferred after diaphragmatic injury and was subsequently successfully completed.

One of the first patients enrolled suffered a fatal thromboembolic stroke 24 hours after the surgical procedure. He was eating breakfast 18 hours post-operatively when the stroke occurred. Following this case our practice changed regarding anticoagulation. A further patient had transient facial weakness post-surgery. Signs of cerebral ischaemia were detected on an MRI scan, but a CT Head scan was negative for stroke.

3.4.5.2 *2nd Stage Electrophysiological Catheter Study*

There have been no intra-procedural complications with the catheter 2nd stage. One patient who required right atrial ablation for a focal atrial tachycardia was found to have prolonged symptomatic sinus pauses after the procedure and required a permanent pacemaker prior to discharge. Another patient subsequently developed persistent symptomatic sinus bradycardia and also required a pacemaker.

3.5 Discussion

This series is of a highly symptomatic group of patients with long-standing persistent atrial fibrillation for whom catheter ablation alone has traditionally provided poor long-term outcomes. It is more homogenous in this respect than previously published studies of hybrid ablation. The heterogeneity of previous hybrid ablation series and difficulty in interpretation of their results has been highlighted^{186,187}. The intensity of monitoring during follow-up has also been variable in reported series. The outcomes from this series appear superior to the outcomes from catheter ablation alone in the treatment of longstanding persistent atrial fibrillation. This could point to a more durable lesion set or it may be that the benefit lies in more effective ablation of epicardial triggers of AF such as ganglionic plexi. It will not be until robust long-term (5 year) outcome data is known that it will be possible to fully evaluate the value of this technique.

The first Cox-Maze surgical technique is now 30 years old and long-term outcomes of this and the subsequent Cox-Maze III procedure performed on cardio-pulmonary bypass remain excellent^{184,185,183,161,184,185}. The development of the Cox-maze IV technique in 2004, incorporated minimally invasive thoracoscopic surgical techniques which could be performed without cardio-pulmonary bypass. These techniques failed to match the Cox-maze outcomes however and hybrid ablation techniques incorporating either simultaneous or staged electrophysiological study¹⁷⁴ were

developed. Three techniques for hybrid ablation have been reported; the thoracoscopic encircling catheter, the bilateral clamp technique and the subxiphoid pericardioscopic procedure. Outcomes for persistent and long-standing persistent atrial fibrillation in the bilateral clamp studies is up to 88.2%¹⁸⁹ and 87.7%¹⁹⁰ freedom from AF symptoms off anti-arrhythmic drugs. Because of the demanding learning curve in performing this procedure its widespread application has remained limited.

Previous studies of the thoracoscopic encircling catheter described above have produced widely differing outcomes. In Le Meir's series of 19 patients, only 7/19 (36.8%) of all AF patients and 4/14 (28.6%) of persistent AF patients remained arrhythmia free at one year¹⁹¹. In comparison Bisleri et al report 40/45 (88.9%) of persistent atrial fibrillation patients free of symptomatic arrhythmia at one year.

Published studies of the sub-xiphoid approach have all described convergent procedures. Multi-centre series in persistent and long-standing persistent patients have reported 52% of patients arrhythmia free off anti-arrhythmic drugs and 76% with¹⁹⁴. More recently, one year freedom from AF of 86% on anti-arrhythmic drugs and 62.2% off has been described¹⁹⁵.

All of the hybrid techniques have a higher complication rate than published series of catheter ablation¹⁸⁶ but the unilateral VATS approach described above does appear to have a more favourable risk factor profile when compared to the bilateral VATS or sub-xiphoid approach. The most common complication in this series is phrenic nerve palsy that, although mostly transient, has been associated with a symptomatic deterioration in some patients. In response to these findings surgical practice was changed to incise the pericardium further from the phrenic nerve, decrease the tension on the pericardial stay sutures and irrigate the pericardium with normal saline during ablation delivery to reduce thermal injury to the phrenic nerve.

There was one fatal stroke early in this series and anticoagulation protocols were changed in response to aim for an INR of 2.0 if the patient is on Warfarin or continue any direct oral anti-coagulation up to 48 hrs prior to surgery. Heparin is administered at the time of ablation (ACT>300 secs), is not reversed and anticoagulation restarted in the form of the direct oral anti-coagulant Dabigatran in all patients on the evening post surgery.

It is highly beneficial, for there to be a close working relationship between cardiac surgeons and electrophysiologists in both the initial AF heart team discussions and also in monitoring during follow-up and outcome data collection. Patients need to be made aware that this is a two-stage process with the initial surgical procedure unlikely to be enough to maintain sinus rhythm. This is borne out in our results and it is essential patients are clearly informed of the duration of treatment and commitment to the whole process.

As our study and others demonstrate, surgical ablation carries higher risks than catheter ablation. It is therefore important that surgical AF ablation and hybrid AF ablation provide better outcomes if this technique is to continue to warrant its place in the international guidelines for Atrial Fibrillation Management for longstanding persistent atrial fibrillation.

3.6 Conclusions

The staged hybrid approach described here with left atrial posterior wall isolation and a right atrial cavo-tricuspid isthmus line appears to give superior outcomes at one year to published outcomes of longstanding persistent atrial fibrillation patients undergoing catheter ablation^{138,232}. Robust long-term 5 year outcome data is needed along with randomised control trials focusing on comparing surgical, hybrid and catheter techniques all aiming for the same lesion set. The question of whether

hybrid ablation is superior due to the use of epicardial ablation or solely because of a two-stage ablation process also needs to be addressed.

4 Chapter 4 - The effect of atrial fibrillation ablation techniques on P wave duration and P wave dispersion

4.1 Abstract

Background: A reduction in surface ECG P wave duration dispersion is associated with improved outcomes in atrial fibrillation ablation. We investigated the effects of different ablation strategies on P wave duration and dispersion, hypothesising that extensive LA ablation with left atrial posterior wall isolation would give a greater reduction in P wave duration than more limited ablation techniques.

Methods: A retrospective analysis of ECG's from patients who have undergone AF ablation was performed and pre-procedural sinus rhythm ECG's were compared with the post procedure ECG's. Maximal P wave duration was measured in leads I or II, minimum P wave duration in any lead and values were calculated for P wave duration and dispersion. Left atrial dimensions and medications at the time of ECG were documented. Ablation strategies compared were; pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (PAF) and the persistent AF (PsAF) ablation strategies of pulmonary vein isolation plus additional linear lesions (Lines), left atrial posterior wall isolation via catheter (PWI) and left atrial posterior wall isolation via staged surgical and catheter ablation (hybrid).

Results: Sixty-nine patients' ECG's were analysed: 19 PVI, 21 Lines, 14 PWI, 15 Hybrid. Little correlation was seen between pre-procedure left atrial size and P wave duration ($r = 0.24$) but LA size and P wave duration was larger in PsAF patients. A significant difference was seen in P wave reduction driven by Hybrid AF ablation ($P < 0.005$) and Lines (<0.02). There was no difference amongst P wave dispersion between groups but the largest reduction was seen in the hybrid ablation group.

Conclusion: P wave duration increased with duration of continuous atrial fibrillation. Hybrid AF ablation significantly reduced P wave duration and dispersion compared to other ablation strategies including posterior wall isolation via catheter despite this being the same lesion set.

4.2 Introduction

Prolonged P wave duration on a standard surface ECG has been associated with the development of atrial fibrillation²³⁴²³⁵²³⁶ and AF recurrence following catheter or hybrid ablation. Conversely a reduction of P wave duration has been associated with favourable outcomes following ablation of atrial fibrillation²³⁷²³⁸²³⁹

P wave dispersion is the difference between the longest and shortest P wave duration on a surface ECG²⁴⁰²⁴¹²⁴² and prolongation is associated with atrial fibrillation development in coronary artery disease and post cardiothoracic surgery²⁴³²⁴⁴ as well as a number of other clinical situations²⁴². Reductions in P wave dispersion are associated with favourable outcomes following AF ablation²⁴⁵.

The cause of P wave prolongation is complex but intra atrial conduction delay or block due to structural, neurohormonal or autonomic mechanisms have been implicated²⁴² while shortening of the P wave duration and P wave dispersion following AF ablation has been proposed to be due to structural atrial changes²⁴⁶.

International guidelines recommend ablation for drug refractory AF and a wide range of approaches exist²⁴⁷. Improved outcomes are associated with P wave shortening for both paroxysmal and persistent AF in a variety of lesion sets²³⁷²⁴⁸²⁴⁹. Pulmonary vein isolation (PVI) is the established lesion set for paroxysmal AF but the optimal ablation strategy for persistent atrial fibrillation ablation is undefined²⁵⁰. The STAR AF 2 trial showed that the addition of linear ablation or the targeting of complex fractionated atrial electrograms provided no increased survival from AF than PVI alone¹³⁸. An alternative approach is the “box lesion pattern”, involving complete isolation of the

pulmonary veins and posterior wall of the left atrium, done via catheter or surgical ablation which has shown promise in the treatment of persistent atrial fibrillation although randomised data is lacking¹⁹⁶²⁰⁹¹⁸⁷¹⁶¹.

4.3 Aims

In this retrospective study P wave duration on the surface ECG was compared pre and post ablation in paroxysmal atrial fibrillation patients following pulmonary vein isolation and persistent atrial fibrillation patients who have undergone either catheter ablation or a combined surgical and hybrid ablation. The hypothesis is that more extensive ablation will result in greater change in P wave duration and dispersion. It would then follow that left atrial posterior wall isolation would be associated with the greatest shortening of P wave duration and P wave dispersion due to greater atrial structural and substrate modulation than more limited lesion sets.

4.4 Methods

This was a retrospective study of patients undergoing atrial fibrillation ablation at Derriford Hospital, Plymouth from 2012-2016. Four different ablation approaches were compared:

1. Pulmonary vein isolation (PVI)

This is the standard lesion set for patients with symptomatic paroxysmal atrial fibrillation. Cases in this study were performed by two different operators via radio-frequency ablation with contact-force catheters using either the CARTO (Biosense-Webster, Diamond Bar, California, USA) or Velocity (St Jude Medical, St. Paul, Minnesota, USA) systems.

2. Pulmonary vein isolation with additional linear ablation, roof and/or mitral isthmus lines but without left atrial posterior wall isolation (Lines)

This lesion set was used for patients with symptomatic persistent atrial fibrillation. In these twenty-one cases the lesion set was created with radio-frequency ablation using CARTO (Biosense-Webster, Diamond Bar, California, USA) with contact-force sensing catheters in nine patients and phased array PVAC and TVAC catheters (Medtronic, Minneapolis, Minnesota, USA) in twelve cases.

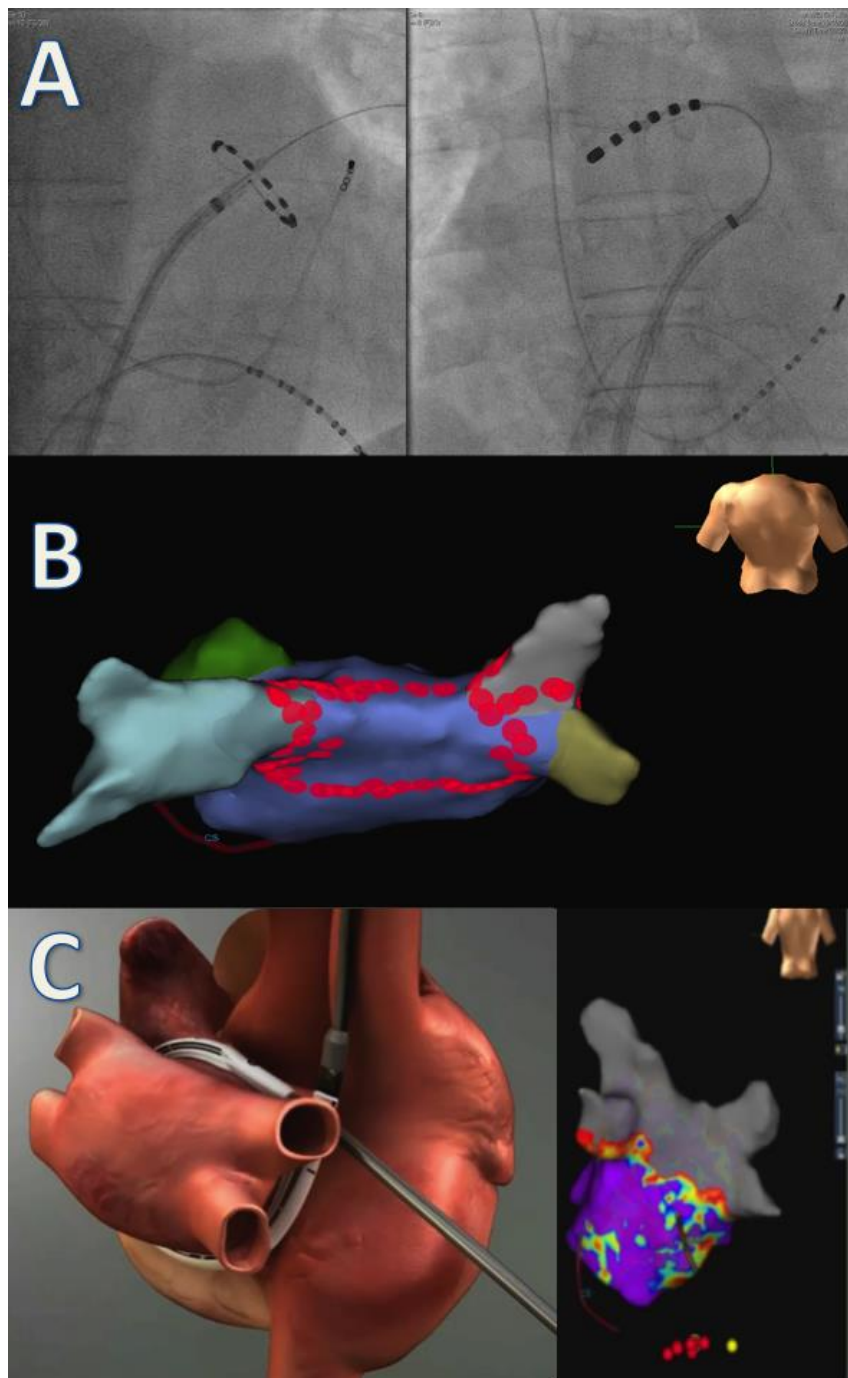
3. Left atrial posterior wall isolation via catheter with PVI + roof and floor lines (PWI)

This lesion pattern was used for later patients with symptomatic persistent atrial fibrillation using either the CARTO or Velocity (St Jude Medical, St. Paul, Minnesota, USA) systems with Smart-touch (Biosense – Webster, Diamond Bar, California, USA) or Tacticath (St Jude Medical, St. Paul, Minnesota, USA) catheters and contact force availability.

4. Two-stage non-concomitant hybrid ablation (Hybrid)

This procedure is offered to patients with long-standing persistent atrial fibrillation (continuous AF duration of greater than one year). It involves a surgical epicardial stage to isolate the left atrial posterior wall and target ganglionic plexi using the Cobra Fusion device (Atricure Inc, Minneapolis, US) with a later catheter ablation stage to confirm and re-isolate the left atrial posterior wall if required using the Velocity system (St Jude Medical, St. Paul, Minnesota, USA).

Figure 4-1 Creation of the lesion sets in the study. *Panel A* shows the PVAC catheter on the left and TVAC catheter on the right. This was used in 12/21 cases to isolate the pulmonary veins and perform linear ablation. *Panel B* shows the final lesion set following left atrial posterior wall isolation via catheter ablation using the Velocity system. *Panel C* demonstrates the two stage hybrid ablation process whereby on the left the left atrial posterior wall is isolated first by epicardial ablation using the Cobra Fusion device. Patients then return for electroanatomical mapping and further ablation to complete isolation if required. The image on the right shows an isolated left atrial posterior wall.

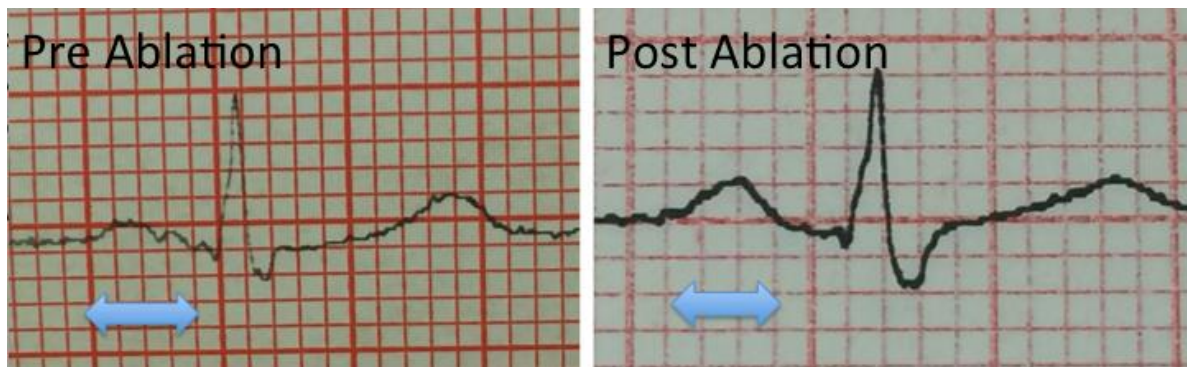


As this study was a retrospective observational study of anonymised ECG's formal ethical approval was considered to be unnecessary and was not sought.

Patients were identified from local registries of ablation procedures from two different operators. Hospital notes were then searched for twelve-lead ECG's in sinus rhythm prior to the ablation procedure and ECG's taken immediately after the procedure. Where multiple ECG's were available those closest to the ablation procedure were used. If the patient was in atrial fibrillation at the time of ablation the most recent ECG in sinus rhythm prior to the ablation was used. Details of left atrial dimensions and antiarrhythmic medication were documented at the time of the ablation procedures and recorded from the notes.

Measurement of maximal P wave duration on the ECGs was taken from the limb leads II or I using callipers and a rate ruler. All the ECGs used had been recorded at standard ECG settings of 25mm/s and 10mm/mV. One investigator identified and selected the ECGs as well as making the initial measurements of maximal P wave duration. The ECGs were then anonymised and randomised before being re-measured by three further investigators blinded to the initial results, ablation approach and timing of the ECG. At this stage an additional measurement of the minimal P wave duration in any lead was calculated in the anonymised ECGs and a measurement of P wave dispersion was made by subtracting the largest P wave in the limb leads (I or II) from the shortest P wave duration in any lead. This resulted in four measurements of maximal P wave duration and three measurements of P wave dispersion for each ECG. The change in P wave duration and P wave dispersion pre and post ablation was calculated for each procedure and a mean value calculated for each procedure.

Figure 4-2 Reduction in P wave duration seen on a surface ECG pre and post AF ablation (Lead II, 25mm/s, 10mm/1mV)



The P wave duration, P wave reduction post ablation and the P wave dispersion measurements were compared for each ablation approach.

4.4.1 Statistical Analysis

Values given are mean (+/- standard deviation) unless stated otherwise. Change in P wave was compared between pre ablation and on the first ECG post procedure for each group with the Kruskal Wallis test used to analyze variance between groups and a using Wilcoxon Signed Rank Test used to compare interventions as the data was not normally distributed (Shapiro-Wilks test on change in P wave duration $p=0.07$). Correlations between P wave change and left atrial AP diameter were examined using the Spearman correlation. Statistical analysis was performed using the R statistical package version 3.2.2 (The R project).

4.5 Results

Eighty-five procedures were identified from the registries of the different AF ablation approaches; of these only sixty-nine patients had usable ECG's available from before and after the procedure. This resulted in nineteen in the PVI group, twenty-one in the Lines group, fourteen in the PWI and fifteen in the hybrid group. The patients who underwent PVI were all paroxysmal atrial fibrillation patients, whereas those in the Lines, PWI, and hybrid groups all had persistent atrial fibrillation. All of the Hybrid group had longstanding persistent atrial fibrillation with continuous atrial fibrillation durations or greater than one year.

The increasing duration of atrial fibrillation was reflected in an increasing left atrial size between groups from PVI to Hybrid and also an increasing initial P wave duration from PVI to hybrid. There was little correlation between P wave duration and left atrial AP diameter ($r = 0.2475$). No difference was seen in medications between ECG recordings as patients had antiarrhythmic medications continued up until the ablation procedure and were taking these drugs when the post-ablation ECG's were recorded on the day of procedure.

The findings of left atrial AP diameter, P wave change and P wave dispersion can be seen in Table 1.

Table 4-1 Summary of P wave changes between ablation techniques

Ablation Technique	Number of patients	AF syndrome	Pre procedure Left atrial AP diameter (mm)	Pre procedure maximal P wave duration (ms)	Pre Procedure P wave dispersion (ms)	Mean change in P wave duration	Median Change in P wave duration (IQR)	p value	Mean change in P wave dispersion (ms)	Median Change in P dispersion (IQR)
PVI	19	Paroxysmal AF	36.79	114	58.5	0.66	5 (-7.1-14.2)	p =0.88	-2.37	-2.37 (-10-10)
Lines	21	Persistent AF	42.25	123	64	-10.51	-10.51 (-25- 2.5)	p <0.02	-7.71	-10 (-20 - 10)
PWI	14	Persistent AF	39.64	118	51	-7.86	0 (-21.7 - 0)	p = 0.21	-6.86	0 (-33 - -6.9)
Hybrid	15	Longstanding Persistent AF	46.2	133	69	-27.45	-37.5 (-50 - -3.75)	p<0.005	-22.07	-28.5 (-36.8 - 6.25)

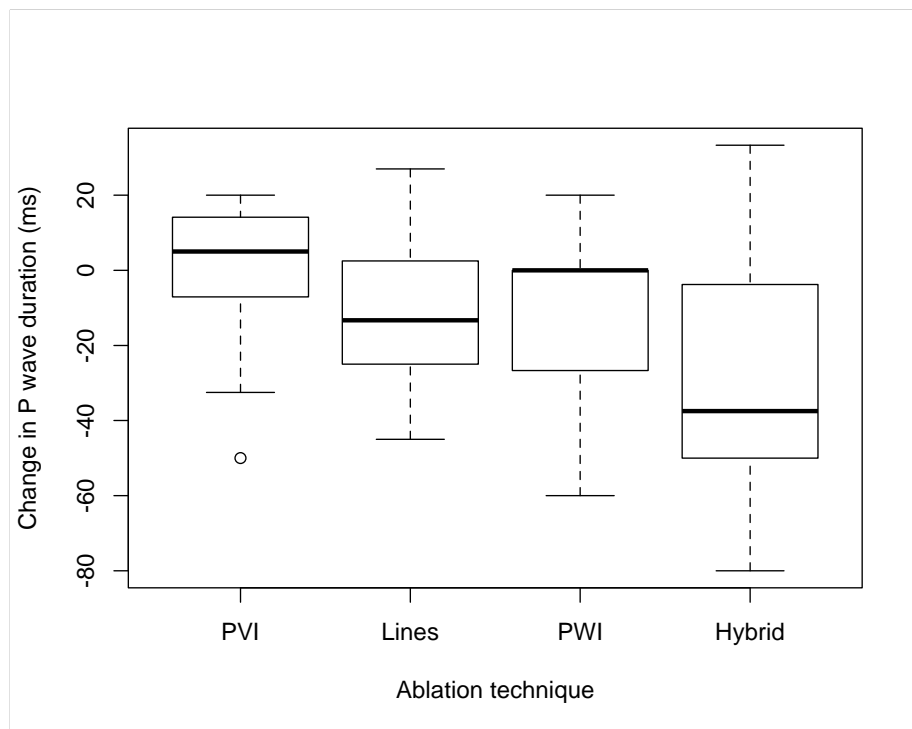
4.5.1 Intra-observer variability

One-hundred and twelve measurements of maximal P wave duration were recorded by all four observers. As minimal P wave duration was measured only by the three blinded observers they made a further 154 measurements on the study ECG's. The intraclass coefficient (ICC) statistic for the four observers was 0.58 (95% CI: 0.46-0.67) and when the same lead was used by each observer the reliability improved with an ICC statistic of 0.63(95% CI:0.5-0.74).

Correlation between the blinded measurements was excellent. Two-hundred-and-seventy-six measurements of maximal or minimal P wave duration were made by each of the three observers with a calculated ICC statistic of 0.8 (95% CI: 0.72-0.86).

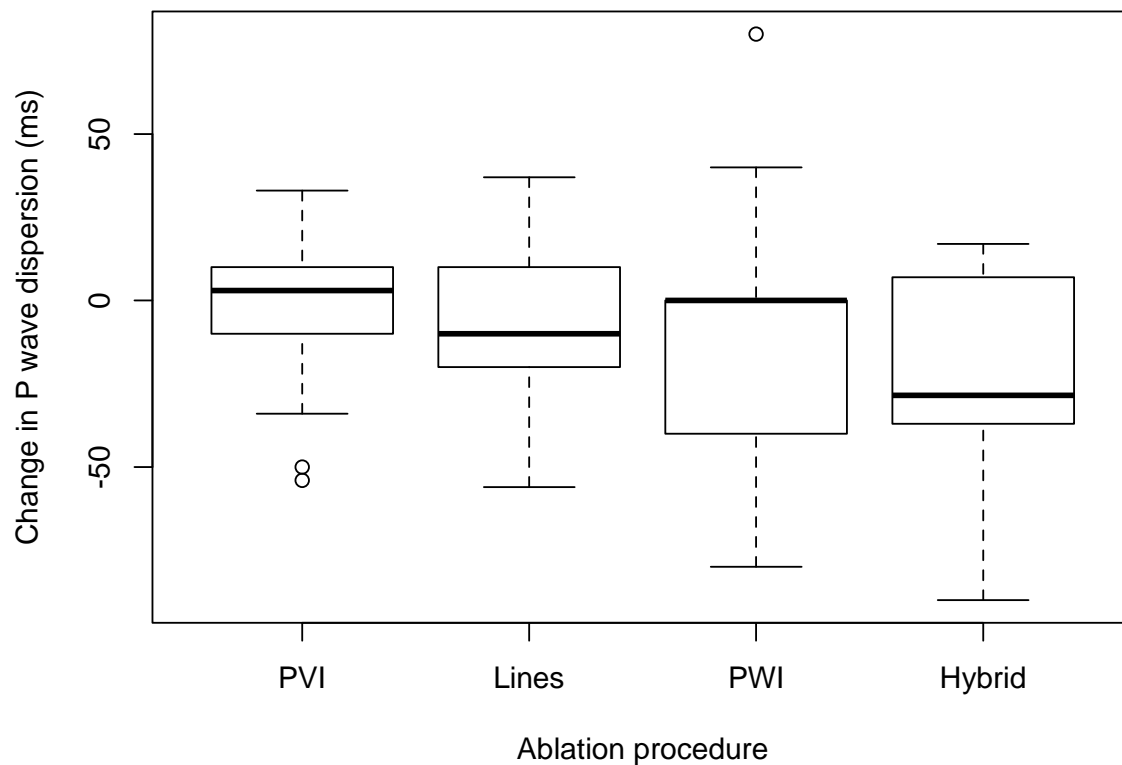
4.5.2 P wave duration

A significant difference was seen in the change in mean P wave duration between groups (Kruskal-Wallis rank sum test $p = 0.016$). Hybrid ablation produced the largest reduction in P wave duration, followed by the Lines group, PWI and then PVI. There was a trend towards statistical significance comparing the Hybrid group against Lines ($p=0.076$) and PWI ($p = 0.06$) but significance was only met compared to PVI alone. ($p= 0.005$). The Lines group had the next most significant reduction in P wave duration and this was again statistically significant against the PVI group ($p=0.04$) but not against PWI ($p= 0.35$). (Fig 2)

Figure 4-3 Box plot of change in mean P wave duration following ablation

4.5.3 P wave dispersion

The Kruskal-Wallis test did not suggest a significant difference between groups ($p = 0.44$) but again there was a greater reduction in mean P wave dispersion with complexity of ablation from PVI to Hybrid ablation, which resulted in the largest decrease in P wave dispersion. The Hybrid group was the only approach to achieve a statistically significant difference when compared against the combined other three approaches ($p = 0.02$).

Figure 4-4 Box plot of change in mean P wave dispersion following ablation

4.6 Discussion

In this study the association between different ablation strategies and changes in surface ECG P wave duration and P wave dispersion following ablation was investigated. The hypothesis was that more extensive ablation would lead to greater change in P wave duration. These simple measurements have been shown to be easily measured on a standard 12 lead ECG²⁴⁰ and prolongation of both has previously been shown to be associated with the development of atrial fibrillation^{236 234} while reductions of P wave duration and dispersion following catheter ablation confers better outcomes²⁴⁵²⁵¹²⁵².

This study demonstrates that measurements of P wave duration on standard ECG's can be reliably and reproducibly analysed. There was fair to good correlation between all four observers, which was improved when the same ECG lead was used. Correlation amongst the three observers who made blinded measurements was excellent. Given that standard ECG's were measured with the need to round measurements up or down to the nearest 10ms it is to be expected that some intra observer variability was seen. For further study it may be that measuring ECG's at 50mm/s rather than the standard 25mm/s would improve accuracy and even result in improved correlation.

As in previous studies²³⁸, P wave duration in this study was associated with the duration of atrial fibrillation and increased from patients with paroxysmal atrial fibrillation to patients with persistent and longstanding persistent atrial fibrillation. Left atrial size also increased between these groups but no correlation was seen between the left atrial AP diameter and P wave duration suggesting structural changes alone do not account for p wave prolongation.

The largest reduction in surface ECG P wave duration following ablation was seen in the Hybrid ablation group but a significant reduction was also demonstrated in the group who underwent pulmonary vein isolation with linear ablation (roof and mitral isthmus ablation). Hybrid ablation alone resulted in a significant reduction in P wave dispersion when compared to the other ablation approaches. This supports the findings from previous studies that reductions in P wave duration and P wave dispersion are seen following AF ablation but the study was not designed to obtain follow-up to provide outcome data in these groups.

The mechanism determining P wave duration is not known but is most likely due to a complex series of factors including structural changes in the atrium, atrial fibrosis, intra –atrial conduction time and autonomic innervation^{24,72,52}. The findings of this study would suggest that more extensive ablation is linked with greater reduction in P wave duration but the confounding factor is that P wave duration

increases with duration of atrial fibrillation and longer durations of atrial fibrillation have more complex ablation strategies.

The greatest change in P wave duration and P wave dispersion was seen in the Hybrid group. The left atrial posterior wall isolation lesion set in the Hybrid and PWI groups was identical and the main difference between them is the surgical epicardial ablation and ganglionic plexi excision in the Hybrid group. although greater lesion durability and a more intact “box” lesion pattern could be inferred from chapters 2 and 3.

One claimed advantage of surgical ablation over catheter ablation is that ganglionic plexi can be directly targeted and excised which may result in greater autonomic modulation¹⁵⁴. In this study P wave duration was longer in the Hybrid group at baseline but greater reductions in P wave duration and P wave dispersion were seen in this group compared to the PWI group. No measurement of autonomic modulation was made in these cases but autonomic triggers for atrial fibrillation are well described. Studies have shown that targeting ganglionic plexi, which can be mapped endocardially and targeted by catheter ablation can improve outcomes of atrial fibrillation ablation^{25,32,54,148}. Changes in autonomic innervation have also been shown to effect the P wave on a surface ECG²⁵⁶ while P wave prolongation has been demonstrated in spinal injury patients with autonomic dysfunction who had a subsequent increased risk of AF²⁵⁷ and also diabetics with neuropathies²⁵⁸.

The association between epicardial ablation, ganglionic plexi excision and changes in P wave duration and P wave dispersion warrants further study. If these are surrogate markers of autonomic modulation then it may be that where P wave duration or dispersion is shortened by catheter ablation from any approach it is due to ablation of autonomic triggers rather atrial substrate modulation. This could provide a novel measurement to assess the degree of autonomic modulation following a catheter or surgical ablation as well as give an indication of the likelihood of AF

recurrence. Further research could lead to alternative ablation end-points or follow-up strategies for patients whose P wave duration remains prolonged.

4.6.1 Limitations of the study

This is a small retrospective observational study in which baseline P wave duration varied between groups. Longer pre-ablation P wave duration may allow for greater P wave shortening with ablation. I have not made a direct randomised comparison between ablation techniques and the mean post procedure P wave duration is similar across all groups. There is a greater change in P wave dispersion with a lower post procedure value after hybrid ablation than seen in other groups but this is again non-randomised data that may be susceptible to unrecognised confounding factors.

The ECG measurement of P waves was limited by the retrospective study design in which only standard ECG's were available. Greater accuracy may be shown by either using ECG's at 50mm/s speed or automated measurement. It may also have been possible to enlarge the ECG's for measurement. Due to the use of standard ECG's the measurement of P wave duration was always to the nearest 10ms.

4.7 Conclusions

P wave duration and P wave dispersion increased with duration of continuous atrial fibrillation from paroxysmal to long-standing persistent atrial fibrillation. Hybrid AF ablation was associated with the largest reduction in P wave duration post ablation and was the only technique associated with a significant decrease in P wave dispersion. We hypothesise that the greater reduction in P wave dispersion is due to autonomic rather than substrate modulation.

5 Chapter 5 – Minimally invasive assessment of posterior wall

isolation: The use of oesophageal catheters to check for posterior wall isolation

5.1 Abstract

Background: Left atrial posterior wall isolation (LAPWI) via catheter, surgical and hybrid techniques is a promising treatment for persistent atrial fibrillation (PersAF). We investigated whether confirmation of LAPWI can be achieved using an oesophageal pacing and recording electrode.

Methods: Patients undergoing PersAF ablation with the intention to achieve LAPWI were enrolled. Two approaches to LAPWI were tested: 1) ablation using endocardial catheter ablation only, 2) ‘Staged Hybrid’ ablation with thoracoscopic epicardial ablation, followed by endocardial left atrial electrophysiological study and catheter ablation where necessary. Patients enrolled in the study all required further catheter ablation to achieve LAPWI in this group.

In both groups, oesophageal recording and oesophageal pacing was performed at the start of mapping and electrophysiological study and compared with endocardial electrophysiological findings. This was repeated at the end of the procedure.

Results: Twenty patients (16M, 4F) were studied. Endocardial electrophysiological study showed that in none of the cases was the posterior left atrial wall electrically isolated at the start of the study. One patient with Barretts oesophagus failed to sense or pace from the oesophagus at any point in the study. In the remaining 19/19 oesophageal pacing captured the atrial rhythm at the start of the procedure. LAPWI was then achieved in 17/19 using endocardial catheter ablation; retesting at this point showed sensing and capture of the atrium from the oesophagus was abolished. In the remainder sensing and capture persisted.

Conclusions: Oesophageal pacing can be used to confirm or refute electrical isolation of the left atrial posterior wall.

5.2 Background

The optimal ablative treatment of persistent atrial fibrillation is unclear and outcomes lag behind those achieved in treating paroxysmal atrial fibrillation^{138,231,259}. This has led to the use of lesion sets such as left atrial posterior wall isolation (LAPWI - the 'box' lesion pattern) based on the modified Cox-Maze surgical technique²⁶⁰ created via catheter, surgery or hybrid approaches. Series in persistent and long-standing atrial fibrillation have shown promising results^{207,216,261,262}. (figure 5.1)

Guidelines published in 2016 have given a class IIa recommendation for thoracoscopic approaches utilising the left atrial posterior wall isolation lesion set²²⁹ for persistent atrial fibrillation.

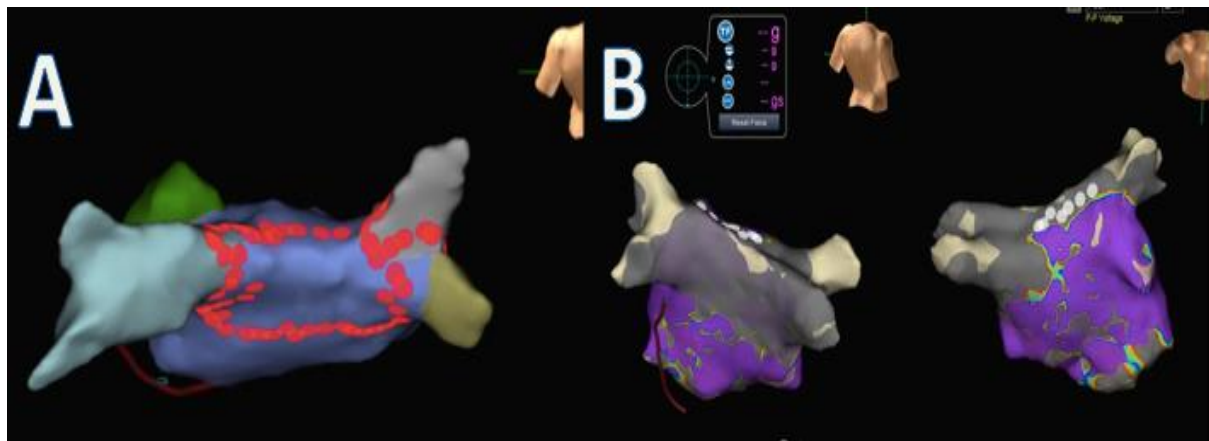
Published studies of two-staged hybrid ablation approaches for AF give varying outcomes from the surgical first stage. The requirement for further ablation to complete the left atrial posterior wall lesion set at the electrophysiological second stage varies significantly from 72%²⁶³ of procedures to as few as 20%²⁶⁴. In all series a significant number of patients undergo an unnecessary second stage electrophysiological study.

5.2.1 Rationale for the study

The oesophagus lies directly behind the heart and is in contact with the left atrium²⁶⁵. It has long been known that the heart can be paced through the oesophagus in emergencies^{266,267,268} and all ablating electrophysiologists are aware of the dangers of oesophageal trauma with left atrial ablation. CT studies have shown that the oesophagus is in contact with the left atrium throughout the cardiac cycle²⁶⁹. It may run a course closer to the right or left pulmonary veins^{265,270}, but it always contacts the posterior left atrium.

Oesophageal temperature probes can be used during left atrial ablation although questions have been raised about the benefit of routine use^{271,272}. They can also be used as a stable reference for 3D mapping systems during the electrophysiological study^{266–268} and some will pace the left atrium.

Figure 5-1 Left atrial posterior wall isolation (including the pulmonary veins) via catheter (panel A) and following the second stage of the hybrid ablation with lesions delivered to the roof line to achieve isolation (panel B)



5.3 Aims

In this feasibility study, we sought to establish whether oesophageal pacing catheters could confirm or refute left atrial posterior wall isolation with entrance and exit block following ablation compared to the 'gold standard' of concurrent intracardiac electrophysiological study.

We aimed to develop a technique that could be of value by potentially allowing verification of the persistence of LAPWI remote from the time of ablation and be of clinical value in staged hybrid AF ablation procedures, identifying those patients who have had the left atrial posterior wall isolated and require no further left atrial ablation. These patients could be saved an unnecessary atrial trans-septal puncture and left atrial study, avoiding exposure to risks that potentially include stroke, tamponade and fatality.

5.4 Methods

Participants were recruited from patients referred to the electrophysiological service at The South West Cardiothoracic Centre, Derriford Hospital, Plymouth, UK. Full ethical approval was granted by the Devon and Cornwall Research Ethics Committee prior to recruitment and all patients gave written informed consent.

All participants in this study were undergoing ablation for drug-refractory, symptomatic, persistent atrial fibrillation. Multi-disciplinary team and patient discussion determined which patients received the staged 'Hybrid' approach and which patients received catheter ablation only.

5.4.1 Methodology of the ablation approaches

5.4.1.1 *Staged Hybrid Approach (Figure 2)*

5.4.1.1.1 The Surgical 1st Stage

The technique for surgical AF ablation utilised the Cobra Fusion Device (Atricure Inc. Minneapolis, USA) through a right-sided VATS under general anaesthetic. This is described in detail in chapter 3.

5.4.1.1.2 Endocardial Electrophysiological 2nd Stage

The second stage procedure is performed a minimum of 8 weeks after epicardial surgical ablation to allow time for conduction to recover at any non-permanent sections of the surgical ablation line. The study is performed under a general anaesthetic via vascular access from the right femoral ± right subclavian/internal jugular veins. It is described in Chapter 2 and 3.

5.4.1.1.3 Oesophageal instrumentation:

An oesophageal pacing and recording electrode ('Box Check' Oesophageal Catheter, Dot Medical Ltd, UK) is passed via the oropharynx (usually nasally) after induction of anaesthesia and the position of the recording and pacing electrodes adjusted to lie as centrally as possible in the area of the left atrial posterior wall using fluoroscopy (Figure 5-2).

5.4.1.1.4 Endocardial instrumentation:

Atrial trans-septal puncture is performed under fluoroscopic guidance using standard orthogonal views and unfractionated heparin is given to maintain an activated coagulation time of greater than 300s. SL1 and Agilis sheaths (St Jude Medical, St. Paul, Minnesota, USA) are passed through the same aperture in the interatrial septum to give access to the left atrial chamber. If the patient is in atrial fibrillation a cardioversion to sinus rhythm was performed.

At this stage in the procedure, the oesophageal pacing and recording study was performed. It was then repeated once LAPWI had been confirmed by endocardial electrophysiological study at the end of the procedure. (Procedural methodology is described in in chapter 2)

5.4.1.2 Catheter Ablation Only approach

All catheter ablation only patients underwent radio-frequency ablation under general anaesthesia. The same oesophageal pacing and recording method was used as in the Hybrid patients described above. The methodology of this technique has been extensively described in chapter 2.

The goal at the end of both approaches was to achieve left atrial posterior wall isolation, confirmed by entrance and exit block into and out of the left atrial posterior wall and by demonstration of pacing and capture within the isolated area without conduction to the rest of the atria.

The oesophageal pacing and recording procedure was performed again at this stage (detailed methodology described below under 'Oesophageal study during electrophysiological study/catheter ablation').

Post procedure, all patients are prescribed one month of proton-pump inhibitors as part of the oesophageal protection protocol post both the catheter only and 2nd stage hybrid ablation procedures.

5.4.1.3 Oesophageal study during electrophysiological study/catheter ablation

Following induction of general anaesthesia, the quadripolar oesophageal electrode (Box Check Catheter, Dot Medical, UK) is passed to an initial 40cm depth via the oropharynx (nasally in 15 of the 20 cases) and screened using fluoroscopy to confirm placement behind the left atrium. The position is adjusted by withdrawing or advancing the catheter until the 2 central electrodes used for pacing and recording are level with the central area of the left atrial image on fluoroscopy (Figure 4). The oesophageal catheter is visible on the 3D mapping system (Velocity/Precision *St Jude Medical* St. Paul, Minnesota, USA) and the position of the initial baseline pacing study is stored. Fluoroscopically, the intervertebral discs and their relation to the two central electrodes used for the pacing and recording is noted. These parameters allow a reference for repeat study following ablation.

As described above, patients in atrial fibrillation following introduction of catheters into the left atrium are cardioverted before EPS is undertaken.

Electrogram sensing and pacing is performed using the middle poles (2,3) and analysed and programmed through the BARD workstation (Boston Scientific, Marlborough, Massachusetts, USA).

Recordings were made of the oesophageal electrograms at the start and end of the left atrial electrophysiological study (EPS) and ablation (figure 5-2). Pacing was performed on the 2 central electrodes of the oesophageal catheter starting at 5mA and increasing incrementally up to 25mA at a rate above the sinus rate until either capture of the atrial rhythm was observed, or 25mA was reached without capture.

Figure 5-2 Oesophageal pacing during catheter ablation. Panel A shows placement of the catheter behind the left atrium just after trans-septal puncture. Panel B shows the end of a case with a circular A-Focus II intracardiac catheter in the left atrium. Panel C shows atrial sensing on the oesophageal channel (OP 1-2, 2-3, 3-4). Panels D and E show the difference pre and post left atrial posterior wall isolation. Sensing is seen in Panel D and failure to capture in Panel E.



5.5 Results

Twenty patients (4 females, 16 males) were studied, 9 had previously undergone the first (surgical) stage of the staged Hybrid ablation approach and 11 underwent catheter ablation only. In two of the catheter ablation patients a clinical decision was made after starting the case not to isolate the left atrial posterior wall, one patient receiving pulmonary vein isolation only and the other a roof and mitral isthmus line only. In these 2 cases we were able to confirm sensing and pacing via the oesophageal catheter at the start of the case and oesophageal study at the end of the case demonstrated ongoing sensing and pacing capture of the left atrium from the oesophagus.

5.5.1 Oesophageal study during electrophysiological study/ablation

In all patients studied, the left atrial posterior wall was not isolated at the start of the procedure. In chapter 3 a relatively low rate of LAPWI as a result of the first stage of the hybrid ablation approach was observed. Of the nine patients who underwent hybrid ablation, four had confirmed left atrial posterior wall exit block following epicardial ablation. However, the posterior wall was not isolated in any case at the start of the electrophysiological study. To complete the lesion set a median of two gaps in the ablation lines needed completion.

In nineteen out of all twenty cases (95%) we were able to pace and sense the left atrium from the oesophageal catheter at the start of the case. The one patient we were unable to pace or sense from the oesophagus was a patient with known Barrett's oesophagus who had previously undergone several gastroscopies, demonstrating scarring and fibrosis in the oesophagus. Failure to capture the atrial rhythm at 25mA was observed in this case despite intracardiac electrograms and pacing showing that the left atrium had not been isolated.

Excluding the patient that we were unable to study and the two patients who did not undergo left atrial posterior wall isolation left seventeen patients. In these we could directly compare the left atrial study with the oesophageal findings before and after LAPWI. All demonstrated clear oesophageal atrial electrograms and capture of the atrial rhythm with oesophageal pacing at the start of the procedure with electrical silence or small 'blunt' electrograms on the oesophageal catheter following ablation and no capture of the left atrium at 25mA@10ms once left atrial posterior wall isolation had been achieved (Table 5-1).

In figure 5-3 panel A the oesophageal pacing impulses can be clearly seen on all channels however despite adjusting the filtering significant artefact was generated across the atrial and coronary sinus electrodes. It is still possible to see atrial electrograms in the coronary sinus and right atrium following the oesophageal impulses. To highlight this in figure 5-3 the oesophageal pacing impulses are indicated with blue horizontal arrows and atrial electrograms are indicated with vertical red arrows.

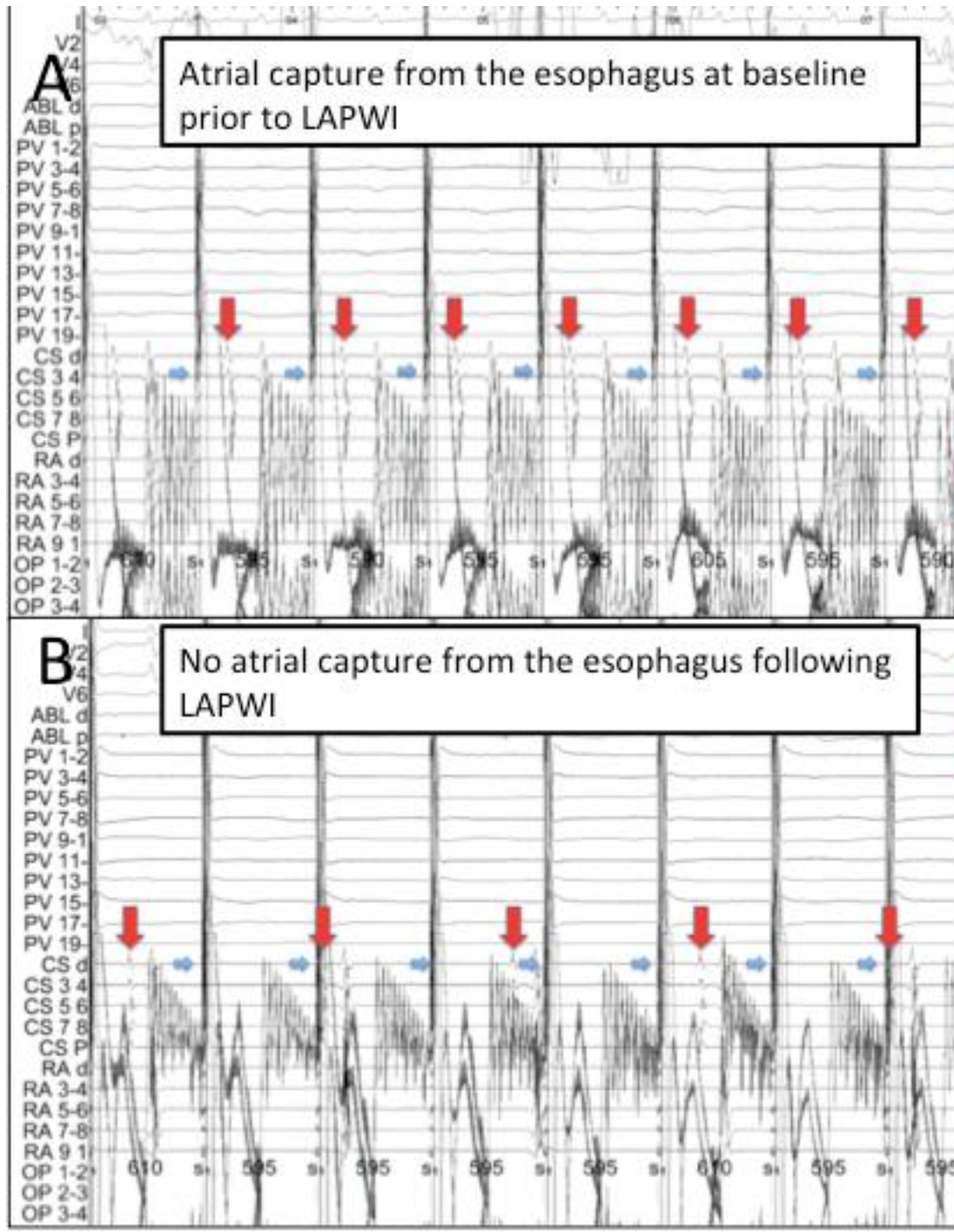
Table 5-1 Summary of Oesophageal pacing during EPS

Patient	Demographic data			Procedure details		Oesophageal pacing (OP) details			Electrophysiological study (EPS) findings post LA posterior wall (PW) isolation			Comments
	Sex	Height (m)	LA diameter (mm)	Study/Arm	AF Ablation	Depth (cm)	Threshold	OP Pace at start of case	PW isolated EPS block	OP PW block	Complications	
1	F	1.66	45	EPS	Catheter	40	10mA@10ms	yes	n/a	n/a	nil	Pulmonary vein isolation only so PW not tested
2	M	1.85	34	EPS	Catheter	43	10mA@10ms	yes	Y	Y	nil	Also had late standalone study
3	M	1.8	45	EPS	Hybrid	42.5	10mA@10ms	yes	Y	Y	nil	
4	M	1.82	55	EPS	Hybrid	45	9mA@10ms	yes	Y	Y	nil	
5	F	1.69	41	EPS	Hybrid	34 (mouth)	10mA@10ms	yes	Y	Y	nil	
6	M	1.77	40	EPS	Catheter	42.5	10mA@10ms	yes	Y	Y	nil	
7	F	1.6	36	EPS	Hybrid	36	10mA@10ms	yes	Y	Y	epistaxis	
8	M	1.8	39	EPS	Catheter	45	8mA@10ms	yes	Y	Y	nil	
9	M	1.8	58	EPS	Hybrid	40	12mA@10ms	yes	Y	Y	nil	
10	M	1.86	32	EPS	Catheter	50	11mA@10ms	yes	Y	Y	nil	
11	M	1.78	45	EPS	Catheter	45	18mA@10ms	yes	Y	Y	nil	
12	M	1.8	50	EPS	Hybrid	46	13mA@10ms	yes	Y	Y	nil	
13	M	1.83	40	EPS	Catheter	42	10mA@10ms	yes	n	n/a	nil	Oesophageal pacing showed atrial flutter. Ablation roof + mitral isthmus lines only.
14	F	1.7	38	EPS	Catheter	40	12 mA@10ms	yes	Y	Y	nil	Also had late standalone study
15	M	1.76	49	EPS	Hybrid	40	10mA@10ms	yes	Y	Y	nil	
16	M	1.65	47	EPS	Hybrid	40	no capture	no	n/a	n/a	nil	Barett's oesophagus with chronic inflammation.

Summary of Oesophageal pacing during EPS findings

Key - LA – Left Atrium, OP – oesophageal pacing, PW – left atrial posterior wall, EPS block – invasive entrance and exit block, OP PW block – oesophageal entrance and exit block.

Figure 5-3 Panel A - Oesophageal pacing at the start of a case with pacing stimuli illustrated by the blue arrows and atrial capture seen on the coronary sinus catheter (red arrows). Panel B - oesophageal pacing failing to capture the left atrium following left atrial posterior wall isolation. Atrial activity is independent of the paced rate. (Pacing stimuli – blue arrows, intrinsic atrial activity – red arrows).



If we include all patients in our analysis, including the one with Barrett's oesophagus, electrophysiology study of all twenty patients studied showed that the left atrial posterior wall was not isolated at baseline. Of those, eighteen patients who underwent successful left atrial posterior wall isolation following catheter ablation we were unable to pace the atrium in any case. Overall the catheter was compared to invasive electrophysiological study forty times (before and after ablation). As a test for left atrial posterior wall isolation where a positive finding was being unable to pace from the oesophagus we had one false positive (being unable to pace the atrium where the LAPW was not isolated) and no false negative results (being able to pace the atrium despite the EPS showing LAPW isolation). This small study gives a positive predictive value of 94.44% (CI 75- 99.98%), sensitivity of 100% (CI 80.49 – 100%) and a specificity of 95% (CI 75.13 – 99.87%). The negative predictive value in this study was 100%.

5.5.2 Complications

The single complication during the study was a short episode of epistaxis occurring during a catheter ablation case. No patients complained of any residual effects of study.

5.6 Discussion

Oesophageal pacing catheters are rarely used outside of paediatric populations for emergency purposes²⁷³. Use in adults is unnecessary for treatment of bradycardia due to the ease of alternative methods of temporary pacing. Likewise the historic use of oesophageal catheters for study of supraventricular tachycardias in adults²⁷⁴ has been superseded by invasive electrophysiology. Yet recently oesophageal electrophysiological study has made a comeback with catheters used for ambulatory monitoring and investigation of atrial fibrillation²⁷⁵. These give superior visualisation of atrial activity compared to surface ECG P waves²⁷⁶ and these studies highlight the tolerability and ease of use of the oesophageal catheters in outpatient settings.

Left atrial posterior wall isolation, the “box lesion pattern”, is a lesion-set based on the Cox-Maze surgical procedure and can be created via catheter, surgical and hybrid atrial fibrillation ablation. Outcomes from series of both catheter ablation²⁰⁷ and surgical ablation^{277,278} are generally better when pulmonary vein isolation (PVI) plus left atrial posterior wall isolation is compared with pulmonary vein isolation plus only a single roof or floor line. This type of lesion set where ablation lines were added to PVI without ‘closing the box’ were studied in the STAR AF II trial (pulmonary vein isolation plus roof and mitral isthmus linear ablation or CFAE ablation) and yielded poor results¹³⁸. Although a meta-analysis of catheter ablation studies of left atrial posterior wall isolation supported the value of the technique²⁶¹, one randomised study comparing PVI plus ‘open’ or ‘closed’ box approaches showed no benefit from posterior wall isolation²⁰⁶. Data is accumulating supporting the value of the ‘box’ lesion set^{216,263} with guidelines supporting left atrial posterior wall isolation with a IIb recommendation¹²¹. However randomised data is limited²⁰⁷ and further research clearly needed.

In this study, we set out to develop a technique of detecting the presence or absence of left atrial posterior wall isolation (‘box set lesion pattern’) from the oesophagus using oesophageal pacing catheters. The results show that it is feasible to use the oesophagus to verify isolation. We have given the positive predictive value based on our results but, as this is an unblinded small feasibility study with only one false positive and no false negatives, further research is required. A larger study is required to determine true positive and negative predictive values of this technique and should necessarily involve oesophageal study blinded to the results of the intracardiac electrophysiological study.

In this study the technique proved to be safe and well tolerated. It was also accurate with initial findings on the oesophageal catheter matching the invasive findings in nineteen out of twenty (95%) consecutive patients who underwent simultaneous study. In patients where LAPWI was achieved at the end of the study, the intracardiac findings agreed with the oesophageal findings in all cases. The

one patient where the technique failed had known Barrett's oesophagus and repeated gastroscopy and biopsy had shown microscopic and macroscopic scarring. We would suggest that Barrett's oesophagus or an alternative condition where fibrosis may be present such as oesophageal strictures should be a contra-indication to oesophageal pacing as a means of electrophysiological study.

Sra et al have shown that the oesophagus is in contact with the posterior left atrium throughout the cardiac cycle²⁶⁹ but may run towards either the left or right pulmonary veins. In every case of our study the oesophageal position allowed study of the left atrium with no patient excluded due to the course of the oesophagus. Larger studies will be required to confirm our findings, but it does appear that the position of the oesophagus does not limit this technique.

Oesophageal pacing potentially offers a quick and safe method of checking the results of a previous ablation. In the hybrid ablation population, where the surgical lesion set involves a single ablation ring incorporating the pulmonary veins, trans-septal puncture and invasive left atrial study may become unnecessary if entrance and exit block from the oesophagus are observed. This could reduce the risk of complications such as tamponade and stroke to the patient, while confirming that the intended lesion set has been achieved. Thus, selected patients undergoing hybrid AF ablation could potentially be studied as out-patients following the surgical first stage and this could also be incorporated into standard follow-up of surgical AF ablation where the intention is to isolate the left atrial posterior wall. We propose a short procedure requiring fluoroscopy and a system analyser for the oesophageal electrode. A method exists to predict the level of the left atrium for oesophageal pacing using patient height ²⁷⁹ but a few seconds of fluoroscopy adds a greater accuracy to the procedure at minimal additional risk. Further study could increase the accuracy of using the oesophageal catheters "blind" but we would currently recommend fluoroscopy in all cases.

5.6.1 Limitations of the Study

This is a small feasibility study of a novel technique. Larger studies may reveal more limitations. The finding that the technique did not work in a patient with significant oesophageal pathology raises the question whether some patients who may have undetected oesophageal abnormalities could produce misleading results, but this situation is likely to be rare. We also found the position of the oesophagus allowed left atrial study in all cases however this may not be the case in larger studies.

Significant artefact was seen during oesophageal pacing which is demonstrated in figure 5-3. We adjusted the filtering in the atrial and CS channels to minimise this, but it was present in all cases. Despite this the electrical artefact did not limit the technique. Further study may highlight greater issues with artefact that limits the utility of oesophageal pacing. However it will also allow refinement of the procedural setup to limit this phenomenon.

In most cases of catheter ablation where LAPWI is achieved, the pulmonary veins are isolated first by wide area circumferential ablation (WACA) followed by performing roof and floor lines. The oesophageal pacing technique appears accurate in determining whether the area of the left atrial posterior wall between the roof and floor lines and the posterior (WACA) lines is isolated. However, reconnection across the anterior aspect of the WACA would not be detected if the posterior part of the encircling lesion between the points of connection to the roof and floor lines remained intact. Thus, it would be possible for a patient to have LAPWI verified by oesophageal study, but have reconnection of a pulmonary vein pair via a break in the anterior WACA line. This possibility would not occur if endocardial linear catheter ablation tools become available which would isolate the whole posterior wall and pulmonary veins as a single 'box' lesion set similar to the surgical approaches.

5.7 Conclusions

Oesophageal pacing catheters can be used to check left atrial posterior wall isolation following atrial fibrillation ablation. Routine use as part of surgical and hybrid atrial fibrillation ablation programmes could allow checking of left atrial posterior wall ablation results without the need for invasive electrophysiological study and its attendant risks. It could also be used for routine follow-up or research study of patients who have undergone catheter, hybrid or surgical AF ablation where the intention has been to electrically isolate the posterior wall of the left atrium.

6 Chapter 6 - Development of an outpatient oesophageal pacing procedure to test for left atrial posterior wall isolation

6.1 Abstract

Aim: To design a technique for outpatient assessment of LAPWI using oesophageal pacing.

Methods: A preliminary study confirmed the feasibility of oesophageal pacing in an outpatient setting using fluoroscopy on a healthy volunteer. Further patients were recruited who were undergoing left atrial posterior wall isolation via catheter or hybrid ablation. Patients who had undergone the lesion set were brought in for standalone study, fasted. An electrode was passed nasally or via mouth to the oesophagus under fluoroscopy and electrograms analysed using a pacing system analyser. Atrial pacing was then attempted. Entrance and exit block from the oesophagus was recorded. If no atrial electrograms were seen and we were unable to pace from the oesophagus LAPWI was assumed.

Results: Eight patients (6M, 2F) were studied without complication. 5 patients had undergone hybrid AF ablation, 3 catheter ablation. The procedure was well tolerated. In 4/8 it was possible to pace the left atrium from the oesophagus, two of these patients had AF recurrence following ablation.

Conclusions: Standalone oesophageal pacing catheters can be used safely and feasibly to follow-up patients who have undergone left atrial posterior wall isolation in the treatment of atrial fibrillation.

6.2 Aims

Oesophageal pacing can be used to check for left atrial posterior wall isolation (LAPWI) and has excellent positive and negative predictive value when compared to concurrent intra-cardiac study as seen in chapter 5. The aim of this study was to design a technique for outpatient assessment of LAPWI using oesophageal pacing.

6.3 Methods

Participants were recruited from patients referred to the electrophysiological service at Derriford Hospital, Plymouth. Full ethical approval was granted by the Devon and Cornwall research Ethics Committee prior to recruitment and all patients gave written informed consent.

All participants in this study were undergoing ablation for persistent atrial fibrillation involving left atrial posterior wall isolation. This was either via a standalone catheter ablation using the 'box' lesion set or the two-stage hybrid ablation described in chapters 2 and 3. Patients selected for outpatient standalone study were selected from patients who had undergone hybrid ablation who had been found at the second stage catheter ablation procedure (greater than 2 months from the surgical ablation procedure) to have complete posterior wall isolation and in whom further left atrial catheter ablation was not necessary.

At the catheter study all patients underwent radio-frequency ablation using the Velocity system (*St Jude Medical* St. Paul, Minnesota, USA) to isolate the posterior left atrial wall or to check and complete left atrial posterior wall isolation as part of the hybrid program. Left atrial posterior wall isolation, when achieved, is confirmed by entrance and exit block into and out of the left atrial posterior wall.

We aimed to develop a technique to assess LAPWI that could be performed while a patient was conscious and be performed in an outpatient clinic. The study was designed for feasibility and built on the study in chapter 4 of oesophageal pacing during electrophysiological study. Results reported included the tolerability and complication rate of this technique. We also compared the findings with the result of the previous ablation where the left atrial posterior wall had been isolated. We did not seek ethical approval to re-study patients undergoing standalone oesophageal study with further invasive electrophysiological study although this may be performed as part of standard clinical care.

6.3.1 Standalone Oesophageal study

6.3.1.1 Preliminary study

Prior to the ethical submission the tolerability of the procedure was tested by myself with the lubricated oesophageal electrode passed nasally (figure 6-1). I was then able to atrially pace myself using a temporary pacing box and check an atrial-pacing threshold which was shown to be 10 mA. The procedure was tolerable, with a warm feeling notable in the centre of the chest during pacing, although the lidocaine lubrication gel used (*Instillagel*) was uncomfortable. Subsequent studies utilized standard lubrication gels with the option of xylocaine pharyngeal spray if significant discomfort was noted.

Figure 6-1 Demonstrating the use of an oesophageal pacing catheter myself and testing a pacing threshold in an outpatient setting.



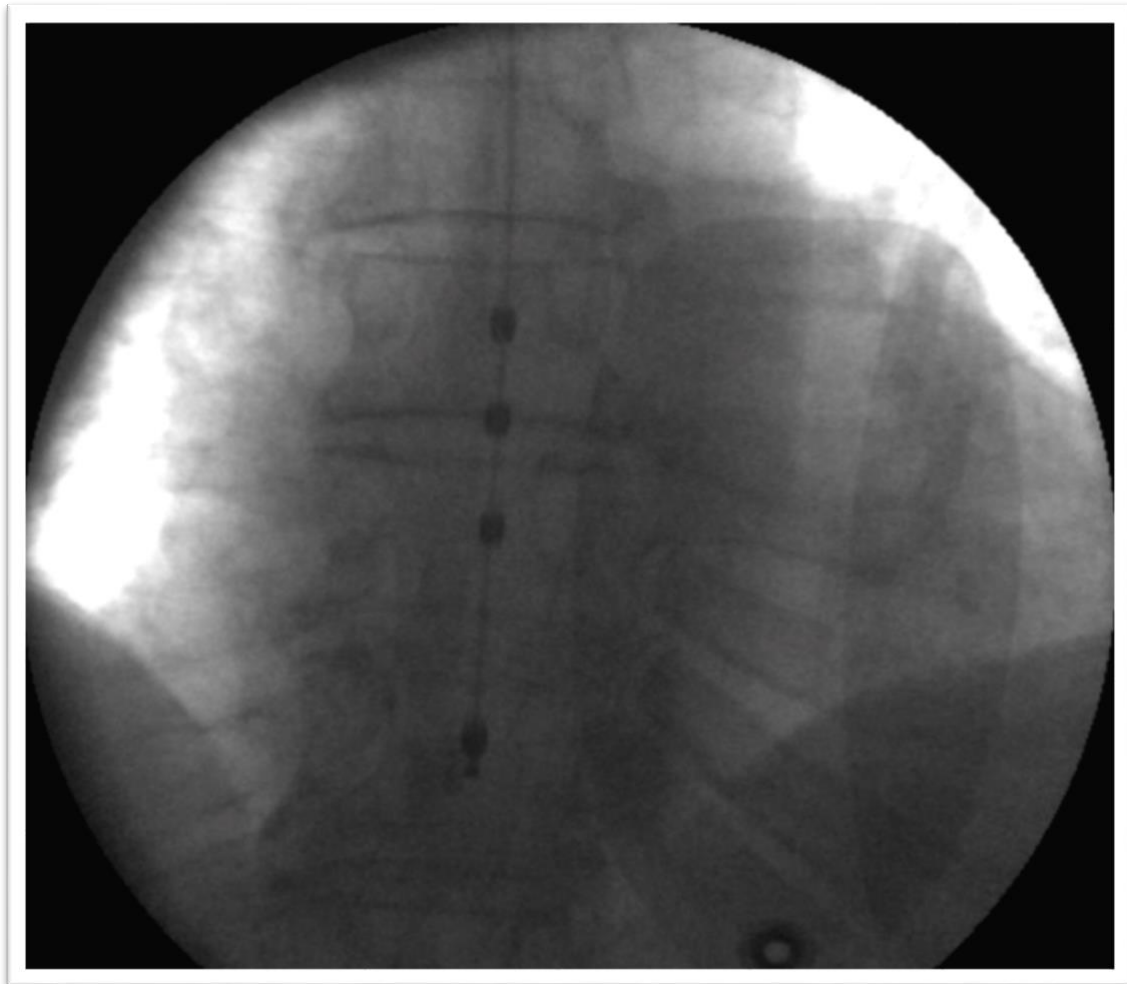
6.3.1.2 Outpatient Studies

All cases were performed with the patient fasted, conscious and without sedation. The oesophageal catheter was passed nasally in all cases with the patient sat up on the bed. Once in position at 40cm depth from the nares the patient lay down on the bed and the catheter was screened with fluoroscopy and adjustments made to place the middle two poles behind the left atrium (Figure 6-2). Three patients who had difficulty swallowing the catheter were able to swallow the catheter once oropharyngeal xylocaine spray was used.

Atrial sensing was achieved by connecting the oesophageal catheter to a pacemaker-system-analyser (PSA) (Medtronic, Minneapolis, USA). A temporary pacing box was used to attempt to pace the heart. Left atrial posterior wall isolation entrance block was assumed to be present if atrial signals were not seen on the PSA when the catheter was in position behind the left atrium. Left atrial posterior wall exit block was assumed to be present if we were unable to capture the left atrium at 20mA@10ms from the middle two poles of the oesophageal electrode (as had been seen in

simultaneous study). Capture of the atrium was determined by acceleration of the atrial rate with pacing as seen on the continuous surface ECG.

Figure 6-2 Fluoroscopy of the oesophageal catheter in a standalone study



6.4 Results

Eight patients were studied as a standalone procedure, two of whom had previously been studied during an ablation procedure.

6.4.1 Oesophageal study as a standalone procedure

The standalone procedure was well tolerated and all patients in the study were able to tolerate the procedure comfortably. Two out of the eight patients required an anaesthetic xylocaine pharyngeal spray but the other patients tolerated the passing of the catheter with lubrication only. No patients required sedation for the procedure.

Of the eight patients who underwent the standalone procedure five had undergone successful left atrial posterior wall isolation via surgical ablation and had not required further ablation at the second stage electrophysiological study. Two patients had undergone left atrial posterior wall isolation but had AF recurrence and one patient had undergone two catheter ablations to achieve left atrial posterior wall isolation and was due surgical closure of an atrial septal defect.

Six of these patients had undergone electrophysiological study previously and the left atrial posterior wall had been shown to be isolated at a study remote from the time of isolation. In five of these, the left atrium was shown to be electrically silent with no sensing from the oesophagus and we were unable to pace the atrium from the oesophagus in the same five. In the two patients who had undergone catheter ablation with the box lesion set but had subsequently developed breakthrough atrial fibrillation we were able to pace the atrium from the oesophagus. One patient had undergone surgical AF ablation only with left atrial posterior wall isolation but remained in sinus rhythm and we were able to sense and pace the atrium. Repeat invasive study of these 3 patients had not yet been performed at the time of this study.

Table 6-1 Summary of standalone oesophageal study patients

Demographic data				Procedure details		Oesophageal pacing (OP) details				
Patient	Sex	height (m)	LA diameter (mm)	Study Arm	AF Ablation	Depth (cm)	Pace with Atrial capture	Threshold	Complications	Comments
1	M	1.74	47	Standalone	Hybrid	40	yes	10mA@10ms	nil	No invasive EPS as DOAC not stopped
2	M	1.81	46	Standalone	Hybrid	47.5	no	no capture @ 20mV	nil	
3	M	1.86	58	Standalone	Hybrid	41	no	no capture @ 20mV	nil	
4	M	1.7	46	Standalone	Hybrid	40	no	no capture @ 20mV	nil	
5	F	1.6	40	Standalone	Catheter	38	no	no capture @ 20mV	nil	
6	M	1.72	39	Standalone	Hybrid	45	yes	10mA@10ms	nil	
7	M	1.85	34	Standalone	Catheter	43	yes	10mA@10ms	nil	Previous EPS study with AF recurrence
8	F	1.7	38	Standalone	Catheter	40	yes	12mA@10ms	nil	Previous EPS study with AF recurrence

Key - LA – Left Atrium, OP – oesophageal pacing, PW – left atrial posterior wall, EPS block – invasive entrance and exit block, OP PW block

– oesophageal entrance and exit block.

6.4.2 Complications

No complications were seen.

6.5 Discussion

Oesophageal pacing catheters are rarely used outside of paediatric populations for emergency purposes²⁷³. Likewise the historic use of oesophageal catheters for study and diagnosis of supra-ventricular tachycardias in adults²⁷⁴ has been superseded by invasive electrophysiology. More recently oesophageal electrophysiological study has been used for ambulatory monitoring and investigation for atrial fibrillation²⁷⁵. The main advantage of the technique is the superior visualisation of atrial activity and P waves when compared to surface ECG's²⁷⁶.

This study was designed to develop a technique of checking left atrial posterior wall isolation from the oesophagus using oesophageal pacing catheters in an outpatient setting. The technique allows for follow-up of patients who have undergone left atrial posterior wall isolation via surgery or catheter ablation. This could be utilized for research purposes or to identify those patient's with reconnections into the posterior wall following ablation and may therefore be prone to late recurrence of atrial fibrillation. In future larger studies it will be important to report on findings at subsequent EP study and rates of AF recurrence where left atrial capture was not possible from the

oesophagus. Previous studies have suggested that incomplete LAPWI is associated with late recurrence of AF²²⁶ and Chapter 2 of this thesis also demonstrated better outcomes with complete LAPWI. More evidence is necessary before further electrophysiological study and ablation could be recommended for asymptomatic patients with positive oesophageal pacing who remain in sinus rhythm. Currently any decision on further invasive study needs a symptomatic justification in addition to the oesophageal pacing findings

The studies performed were uncomplicated and well tolerated. We had initially believed that we would be able to predict the level of the left atrium by using patient height and that visualisation of the catheter via fluoroscopy might not be needed. A technique for this has been described²⁷⁹ but we found it did not accurately predict the depth required for oesophageal pacing as seen in table 6-2 below which includes all cases in chapter 5 and 6.

Table 6-2 Predicted depth of oesophageal pacing by height (all values cm)

Patient Height	Predicted depth	Actual depth	Diff
166	34.5	40	5.5
185	39.25	43	3.75
180	38	42.5	4.5
182	38.5	45	6.5
174	36.5	40	3.5
169	35.25	34	-1.25
177	37.25	42.5	5.25
181	38.25	47.5	9.25
186	39.5	41	1.5
170	35.5	40	4.5
160	33	36	3
180	38	45	7
180	38	40	2
186	39.5	50	10.5
178	37.5	45	7.5
180	38	46	8
183	38.75	42	3.25
170	35.5	40	4.5
176	37	40	3
165	34.25	40	5.75
160	33	38	5

172	36	45	9
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While correlation exists between the patient's height and the depth required to pass the oesophageal catheter, a few seconds of fluoroscopy adds a greater accuracy to the procedure at minimal additional risk to the patient. It may be that further study increases the accuracy of using the oesophageal catheters "blind" but we would currently recommend fluoroscopy in all cases.

6.5.1 Limitations of the Study

This is a small feasibility study of a novel technique. A larger study is ongoing and may reveal more limitations. Our aim in the standalone technique was to develop a technique that could lead to further study and this is clearly required to calculate positive and negative predictive values. It will also be important to compare the standalone study with subsequent invasive EPS.

6.6 Conclusions

Standalone oesophageal pacing catheters can be used safely and feasibly to follow-up patients who have undergone left atrial posterior wall isolation in the treatment of atrial fibrillation. Larger studies are necessary to define a role for this technique and the AF recurrence rate in patients who it is possible to pace the left atrium from the oesophagus.

7 Chapter 7 - The development of new catheter technologies in the ablation of Atrial Fibrillation: Electrical isolation by electroporation of right ventricular myocardium in an ex-vivo beating porcine heart: a potential novel use of the Alert internal cardioversion catheter

7.1 Abstract

Background: Electroporation is a mechanism where the cellular response to large electrical pulses triggers apoptosis. Novel ablation catheters have utilised this technique for ablation in animal models. We sought to establish whether the Alert internal cardioversion catheter could deliver linear ablation lesions via electroporation. The aim of this study was to demonstrate electrical tissue isolation using high-energy biphasic defibrillation shocks delivered in linear lesions via the Alert catheter in beating ex-vivo porcine hearts.

Methods: Two recently recovered porcine hearts were placed in a specialised water bath, perfused and oxygenated ex-vivo to continue beating while the experiments were conducted. The right ventricular free wall was chosen as the site for electroporation due to size, thickness and accessibility. For each heart a temporary pacing box and pacing wires were used to stimulate the heart and pace to 90bpm from the centre of the RV free wall. A suture was placed at the point of pacing to mark the site, the pacing wires removed, and linear lesions delivered to the RV free wall around the suture using the Alert catheter connected to a biphasic defibrillator (Phillips Heartstart

XL). Pacing was then attempted at the site of the suture within the ablation "box" lesion set and outside the electroporation lines. Electroporation was attempted with energies of 200J 100J and 50J.

Results: Using energies of 100J biphasic defibrillation and linear lesions it was possible to isolate a discrete triangular area of the right ventricular free wall on the two experimental hearts with exit block confirmed by pacing inside the isolated areas without conduction out to the surrounding myocardium. Pacing outside the isolated area continued to capture the rest of the myocardium.

Defibrillation at 200J caused steam pops, arcing and discolouration of the myocardium. Following this it was not possible to pace the myocardium even at 20mA10ms one centimetre either side of the ablation line. 50J energy appears insufficient, as it was possible to pace the myocardium following energy delivery. 100J however did not result in steam pops or arcing and it was not possible to capture myocardium when pacing along the electroporation lines.

Conclusions: Electrical isolation of right ventricular myocardium was possible using 100J biphasic defibrillation delivered through an Alert catheter. Further research is needed to investigate lesion size, depth and durability but this is potentially a rapid and simple technique to deliver linear ablation.

7.2 Introduction

Electroporation is a mechanism where the cellular response to large electrical pulses changes the permeability of cell membranes and under the correct conditions triggers apoptosis²⁸⁰. Recent years have seen a number of clinical uses such as using electroporation to allow the opening of cell membrane pores for delivery of genetic material to targeted ablation for malignant tumours^{280–282}. A specific advantage of using electroporation for targeting malignant tissue is the minimising of damage to surrounding structures and tissues²⁸³.

Recent study has shown electroporation to be feasible in animal models for the purpose of cardiac ablation^{284–289}. The speed of the technique and apparent safety with regard to surrounding tissues and structures such as coronary arteries has made this an attractive focus for future catheter ablation development²⁸⁶. No trials in humans have been performed as yet although the technique has similarities to fulguration, an early ablation technique that used higher energies and was consequentially hampered by phenomena such as arcing and barotrauma that led to occasional catastrophic consequences such as cardiac rupture^{290–295}. Fulguration used far higher energies than electroporation and was superseded as an ablation technique by radio-frequency ablation. Contemporary electroporation studies utilize novel ablation catheters and lower energies for ablation in animal models without causing barotrauma to surrounding structures.

7.3 Aims

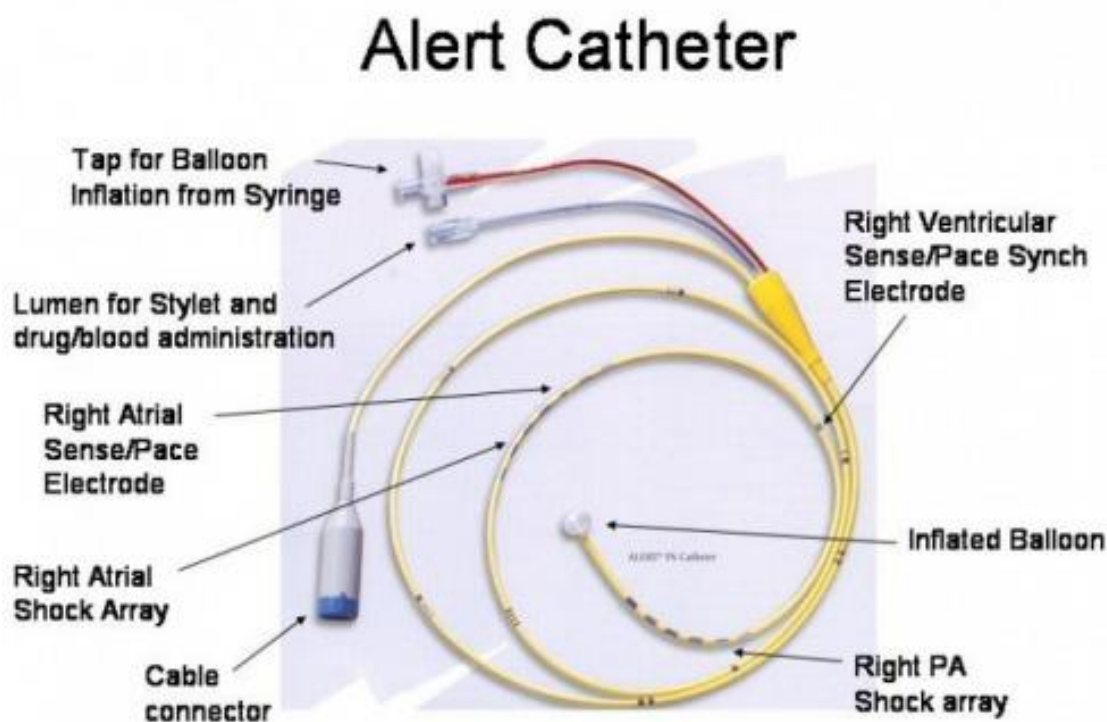
We investigated whether a modified Alert internal cardioversion catheter (Model No AL-SP75149 Dot Medical Ltd, UK) could be used for electroporation. We hypothesised that electrical isolation of an area of ex-vivo porcine myocardium would be possible using an Alert catheter and sought to establish whether a modified Alert catheter connected to a standard high-energy defibrillator would

allow delivery of higher energies through the catheter and following on from this whether the Alert catheter could deliver linear ablation lesions.

7.4 Methods

The Alert catheter is used in conjunction with the Alert Companion system for internal cardioversion and will deliver a maximal energy of 30J. The catheter is designed for internal cardioversion and has a series of six 5mm platinum-iridium bands that make up the distal shock array. Catheters in use for clinical internal cardioversion also include a proximal array with a distal latex balloon however the catheter was modified for this study with the balloon removed. The proximal array and pace/sense electrodes were covered with plastic insulation tape.

Figure 7-1 The Alert catheter. Designed and used for internal cardioversion. For our study the catheter was modified by removing the balloon and covering the right atrial proximal shock array with electrical insulation tape



Our initial experiments focused on designing a setup that would allow the Alert catheter to deliver biphasic shocks in a water bath. A Phillips HeartStart XL biphasic defibrillator was connected to an ECG simulator to allow for a synchronised DC shock. This shock cable was connected to two cables, one of which was connected to a disposable back plate and the other to the Alert catheter. The backpad was placed behind a dummy heart in a shallow water bath. The dummy heart was kept damp and it was confirmed that biphasic defibrillation could be delivered through the distal array of the Alert catheter.

Next we developed a system to deliver shocks ex-vivo on recovered beating porcine hearts. This was done on two separate days with the first day devoted to harvesting a porcine heart and setting it up in our lab to plan the experiments on the second day during which electroporation would be delivered to the porcine hearts.

On the second day three beating hearts were recovered from pigs slaughtered for human consumption. Protocols at the slaughterhouse and laboratory were in accordance with EC regulations 1069/2009 regarding the use of slaughterhouse material for diagnosis and research. The technique used for maintaining, oxygenating and perfusing beating ex-vivo mammalian models originated from Langendorff in 1895 and is well described.

The beating porcine hearts were transported to the laboratory that was setup as described above (figure 7-2). The process took two hours and one heart was not useable after the transfer process. That left us with two hearts on which to conduct the experiments.

Figure 7-2 The setup of the lab for the experiments

The beating hearts were maintained and perfused in the water bath solution and had an intrinsic rate of 60 beats per minute. We then confirmed that pacing was possible using a standard temporary pacing box. Wires placed on the epicardial surface of the heart with positive and negative electrodes spaced 5 millimetres apart. Successful capture was seen when pacing the ventricles and the heart rate rose to the programmed 90 beats per minute.

Of the two hearts we had harvested the right ventricular free wall of the first heart was chosen as the site of our initial electroporation for reasons of accessibility. On the second heart we planned to deliver energy to the atrial endocardium and to do this would require incising the right and left ventricles to gain access to the atria.

The Alert catheter was manually held against the right ventricular myocardium of the first heart so that the array and electrodes at the tip of the catheter were all in contact with the myocardium. As

the optimal energy in our system was unknown we planned DC shocks, synchronised to the ECG stimulator, delivered to the myocardium at 200, 100 and 50 joules to assess the effects and efficacy of each energy level.

If we were able to successfully deliver electroporation via the Alert catheter then we envisaged this producing a linear lesion which if effective would enable us to produce a 'box' lesion pattern to isolate an area of myocardium. An area of the right ventricular free wall was preserved to do this and marked with an epicardial suture. We aimed to demonstrate capture with bipolar pacing at this site initially and measure a pacing threshold before delivering linear lesions to create a box around this central suture. If the linear ablation was successful then we would expect to isolate the myocardium at the site of the suture and pacing at the site of previous capture would fail to pace the heart demonstrating exit block from the isolated area of myocardium.

The second heart was used to repeat the process of electrically isolating myocardium through linear ablation in the same manner as the first heart but instead of using epicardial right ventricular myocardium we aimed to use endocardial atrial myocardium. To facilitate this it was envisaged that the ventricles would need dissecting to access the atrial endocardium. During our initial planning it became apparent that a porcine heart has smaller atria than a human heart and this could make demonstrating electrical isolation in the atrium impossible without formal electroanatomical mapping equipment.

7.5 Results

7.5.1 The first heart

The two Pacing electrodes were manually held against the RV tissue at various sites on the epicardial surface and the heart was seen to be paced at 90 bpm, the rate of the external pacemaker. The

intrinsic rate of the heart was measured at 60 bpm. The pacer current was set at 10mA in demand mode. A suture was placed in the middle of the RV free wall to mark the centre of the intended area of isolation.

Figure 7-3 Pacing the porcine heart



7.5.2 Energy delivery of 200J

The Alert catheter was placed on the epicardial surface of the RV along an imaginary line to the right of the septal wall and after a 10J test shock, a 200J shock was delivered. A loud bang was heard, steam bubbles were seen, and arcing occurred at the point of shock delivery along the line of the catheter array and the heart was stunned. It recovered over a few moments and started to beat slowly again.

The two manual pacing pins were placed on the heart, ostensibly to speed the heart up. It was then noticed that placing the pins along the intended line of lesion prevented capture but placing the pins anywhere else on the heart caused pacing at 90ppm. A line of electrically inert tissue that could not

be paced had been created by the delivery of one 200J shock. This line of isolation went through the heart to the endocardial surface as evidenced by pushing the pacing pins through the myocardium and finding it made no difference to the lack of capture.

7.5.3 Energy delivery at 100J

Given the arcing and barotrauma of the highest energy delivery it was felt that 200J was too much energy and it was decided to reduce the next shocks to 100J in order to prevent arcing and popping.

A second and third linear lesion were made on the surface of the RV using 100J shocks to create a triangular shaped area of isolation which was verified using the manual pacing pins. Outside the isolated area, the tissue was paced at 90ppm and inside the area there was no capture at all. The pacing pins were pushed slowly all the way through the epicardial surface towards the endocardial surface but at no point did the isolated tissue capture the paced pulses.

7.5.4 The second heart

The second heart was still in ventricular fibrillation but the atria were beating regularly at 60bpm. It was decided to create a right ventricular flap in the hope that the ventricular fibrillation may stop. A vertical incision was made to the right of the right ventricular septal wall running from the base towards the Apex and then round and up to create a flap. Unfortunately, the ventricle remained in VF.

7.5.5 Energy delivery to the Atrium

It was decided to open the left atrium and display the Mitral valve from above with the walls of the left atrium exposed. After this surgical opening, the left atrium was still beating even though the walls had been opened and flattened. It was possible to pace the LA from both an anterior flap and a

posterior flap. It was hoped that we would be able to electrically isolate the posterior left atrium via electroporation.

The Alert catheter was placed over a section of the posterior flap and a 100J shock was delivered with the aim of isolating the posterior flap from the rest of the left atrium. Subsequent to shock delivery it was impossible to pace the posterior flap but also not easy to pace the rest of the left atrium. It wasn't clear due to the size of the atrium whether a linear lesion had occurred as pacing would only occur intermittently in the anterior portion of the LA.

7.5.6 50J Energy delivery

It became apparent that the shock or surgical procedure had reverted the RV back to sinus rhythm so attention was switched back to the RV flap which could now be paced at 90ppm at various sites. The Alert catheter was placed on the epicardial surface in a curve with the intention of isolating a section along the anterior left edge of the flap. A 50J shock was delivered which did not isolate this segment. A second 50J shock was delivered which also did not isolate.

A third shock of 100J was then delivered in the same position and the segment became completely isolated. There was no capture in the epicardial, endocardial, or wall section of the intended area for isolation. However, pacing capture was evident at various other sites in the RV. The pacing pins were slowly pushed through the myocardium of the isolated site whilst pacing to demonstrate that isolation was through the full thickness measured at 7mm with a micrometer.

7.6 Discussion

Electroporation is emerging as a promising technique for cardiac ablation^{288,296}. It offers a holy grail for ablating electrophysiologists with the potential for rapid energy delivery to create discrete lines of ablation with minimal trauma to surrounding structures²⁹⁷. A range of uses in clinical medicine

already exists such as the delivery of genetic tissue and the destruction of solid tumours as a cancer treatment. Research in these areas has led to the potential for use in cardiology and we now have a greater understanding of the effects of controlled bursts of energy to cell membranes. The proposed mechanism for electroporation is the that certain energy levels cause permanent opening of cellular channels, influx of calcium into cells and the triggering of apoptosis. This leads to discrete areas of cell death and fibrosis^{280,298}.

A number of animal studies now exist to show that ablation is possible and safe in the limited number of cases published so far^{286–288}. This is in comparison to the historic predecessor of electroporation, the technique of fulguration. Fulguration was superseded by radio-frequency ablation but was at one time used widely as an ablation technology where high energy was delivered directly to the heart. It's major limitation was safety as delivering high levels of energy directly to the heart resulted in steam pops, barotrauma, significant morbidity and mortality^{291,299}. So far the animal studies of electroporation have not shown this.

Our study demonstrates that linear ablation lines can be created by delivery of direct current to epicardial myocardium through a modified ALERT catheter. It would appear from our study that 100 joules was the best energy level of the three that we tested, providing enough energy to create lesions while not producing the steam pops that could cause barotrauma. This may be further refined by more study both ex-vivo and in animal models.

Our assumption is that the ablation lines are created via electroporation but to further test this hypothesis it would be necessary to keep the hearts beating longer and perform histological studies. This was not planned as part of this study and using Langendorff hearts would limit the amount of

histological study possible. The process of electroporation is known to continue after energy has been delivered due to the induction of cellular apoptosis through the opening of cell membrane pores. This may mean that by keeping the hearts beating for longer, rather than recovery of myocardium and the formation of gaps, it may be that ablation lines solidify. This raises the prospect of lower energies causing a delayed apoptosis and being potentially usable and ultimately safer.

It will be important that these experiments are reproduced in animal models where the animals can be recovered and studied at a later date to look for histological changes and assess the degree of recovery or extension of the linear ablation lines. A study similar to those published porcine studies would allow assessment of the width, depth and durability of each lesion plus give safety information.

This study demonstrates that with modification the Alert catheter can deliver higher energies than intended thus making electroporation feasible. In this study it was held manually against the epicardium for the purpose of energy delivery but for the catheter to be used for endocardial ablation it will need a means of control and stability to allow adequate contact. This is likely to be through modification of the catheter itself so that it is steerable but could involve a conventional steerable catheter as a buddy to hold the array in place or an alternative means of fixation to deliver electroporation. Further research and development will be necessary before studies on live animal models are possible.

7.6.1 Limitations of study

This was a small study on two ex-vivo hearts and was designed to test the feasibility of our hypothesis. Due to the small numbers, the limited time we were able to keep the heart beating and the lack of any histology caution is needed about the mechanism durability of electrical isolation.

7.7 Conclusions

Electrical isolation of myocardial tissue can be achieved by delivering single biphasic defibrillator shocks of 100J through the linear array of an Alert catheter. 100J shocks were sufficient to isolate an area in 7mm thick tissue where as 50J was insufficient to isolate 7mm tissue. At higher outputs of 200J steam pops and arcing were seen but a lower output of 50J was insufficient to isolate an area of myocardium. Further study is required to investigate the size, depth and durability of the lesions with histological analysis important in any future studies. Further research will also be necessary to optimise catheter design and energy delivery.

8 Chapter 8 – Conclusions

Atrial fibrillation has been studied for over 100 years and advances in catheter ablation over the past 20 have led to an explosion in available treatments. Despite this, there is much that is yet to be understood. In the introductory chapter I described the competing theories of AF pathophysiology that have ebbed and flowed with time as the science has evolved. It remains unclear what the specific roles of triggers and substrate are that allow the initiation and propagation of the most common arrhythmia seen in human beings. Consequentially it is perhaps inevitable that what to target in AF ablation is uncertain.

Paroxysmal AF in the great majority of patients originates from triggers in the pulmonary veins and therefore the rationale for pulmonary vein isolation is easily understood. Persistent AF is more complex and with a heterogeneous group of patients it is unsurprising that a variety of ablation targets and lesion sets, as summarised in chapter 1, are used. None of these have been shown to be superior to pulmonary vein isolation alone but more complex patients with longer continuous AF durations, left ventricular dysfunction and larger left atria are unlikely to achieve good long-term outcomes with the simplest AF ablation lesion set.

When I originally started the planning for this thesis the intention was to design and run a head to head trial of hybrid AF ablation versus catheter ablation in patients with persistent AF looking at freedom from atrial arrhythmia. This was based around the existing Hybrid AF program in Plymouth. It became clear prior on starting my research that a trial of this size was not going to be feasible in the time available. Instead it was decided to conduct a series of smaller studies to inform a future larger head to head study. The data was intended to be mainly prospectively collected but, as it collected from day-to-day clinical practice at a busy NHS hospital that regularly experienced bed

crises resulting in regular procedural cancellations, this was not possible. Consequentially I used retrospective data for a number of cases in the catheter ablation study. While this only represented 24% of cases (8/33) data had to be collected from notes and I was unable to acquire the information as accurately as I could prospectively.

The technique of oesophageal pacing was not originally a major part of the plan for the thesis but was an idea expanded on early in my research time. After showing it was possible to pace the atrium during an AF ablation procedure, I designed and conducted a study to look at feasibility of the technique and how it could be incorporated into the management of patients undergoing left atrial posterior wall isolation. Oesophageal pacing grew to form a large part of my thesis and is continuing to be studied. A thesis looking at its application alone should be considered by a future researcher.

8.1 Left Atrial Posterior Wall Isolation

In this thesis left atrial posterior wall isolation for the treatment of persistent atrial fibrillation is studied. Chapters 2 and 3 are observational studies looking at current practice at Derriford Hospital Plymouth with left atrial posterior wall isolation via catheter and hybrid ablation respectively. Both techniques result in the same lesion pattern following the catheter ablation alone or the 2nd catheter ablation stage for hybrid ablation.

For a clinical trial comparing the two techniques to be designed it is important to assess the respective outcomes and complication rates for the procedures. Both series demonstrate promising rates of freedom from atrial arrhythmia, which appear marginally higher than the STAR AF II lesion sets¹³⁸ at one year, especially if the lesion set is intact. However, these are non-randomised series of patients in whom the baseline characteristics differ, so caution is required without further studies.

As the practice at Derriford is to offer hybrid ablation to longstanding AF patients with larger left atria one would expect worse outcomes in the hybrid group. For the catheter ablation group in chapter 2 the median left atrial diameter was 40mm (IQR 35-45) with a continuous AF duration of 8 months (IQR 2-12). In chapter 3 for the hybrid group the median left atrial diameter was significantly larger at 46mm (43-49) with a longer continuous AF duration of 24 months (13.75-35.75). Due to the large discrepancy between the groups I chose not to do formal statistical comparison for the ablation outcomes, as these would not have been valid.

These results are further confounded by the impact of two procedures in the hybrid group where an advantage over the single procedure in the catheter cohort should have had specific outcome benefits as gaps in the lesion set from the first procedure can be identified and treated.

As shown in chapter 1 previous small studies of left atrial posterior wall isolation have shown promise compared to pulmonary vein isolation alone. This thesis suggests that it is an encouraging technique but it is important that the lesion pattern is compared to pulmonary vein isolation in larger randomised studies.

8.2 The importance of an intact lesion set and how to maximise ablation success to improve outcomes

The importance of a complete lesion set with confirmed entrance and exit block from the LAPW was demonstrated in chapter 2. Where this was confirmed, 74% remained arrhythmia free at a median of two years follow-up. If repeated consistently this finding would point to a superiority of the lesion pattern over pulmonary vein isolation, albeit in a mixed non-randomised group. As discussed in the introduction, there is variable success in complete LAPW isolation via catheter with the 70% success

rate in chapter two reflective of other contemporary studies. The rates of successful LAPW isolation in the hybrid group were higher and an advantage of a two-staged procedure is that it allows for recovery of the myocardium so that gaps are identified at the second stage and the ablation lines can be touched up and completed. Previous work from HIFU ablation from our group showed an association with long term freedom from AF if the LAPW was isolated²²⁶.

A two procedure strategy has been proposed routinely for pulmonary vein isolation by Das et al who showed re-connection of ablation lines in 26% of pulmonary veins at two months²²⁸. A two-stage strategy for catheter ablation for LAPWI needs consideration but the ethics of repeating electrophysiological study in asymptomatic patients and exposing them to procedural risks is questionable. The counter argument to this is that risks are low from the procedure and if outcomes are better with two stages then they are worth taking. This would be especially true if it was demonstrated that rates of LAPWI are higher after two catheter ablation procedures than one.

Clearly further study is needed to answer this question but there may be a role for oesophageal pacing as described in chapters 5 and 6 to reassess the lesion set following a first ablation both in research trials and clinical practice. This simple technique could be used to identify those patients who are at greater risk of AF recurrence. If the posterior wall is not isolated, then this could trigger a further catheter ablation or identify a cohort of patients who need close observation and follow-up. A prospective observational study looking at LAPWI as identified via the oesophageal catheter two months post catheter ablation should be performed. I would hypothesise, based on this thesis, that the group of patients in whom oesophageal pacing is possible would be at greater risk of recurrence of atrial fibrillation.

I had originally planned to make greater use of the three-dimensional maps created prior to catheter ablation and at the catheter ablation stage of the hybrid group. This could have allowed comparison of low voltage signals and atrial scar pre ablation for the catheter ablation chapter and also following the surgical ablation in the hybrid ablation chapter. Unfortunately, due to a failure to back up the procedures a large proportion of data was lost and could not be recovered in sufficient quantity to make the analysis worthwhile during the period of my study. This is certainly a possibility for future study and as the volume of cases increases with time it would be of great interest to look at burden of atrial scar, it's location and whether it has an effect on outcomes.

The experimental electroporation chapter is not an obvious fit within the scope of this MD thesis. While the thesis was in the planning stages preliminary experiments on modifying the ALERT catheter were conducted. These are described in the introduction of chapter 7. It was hoped that with further evolution of the catheter more studies would have been performed in my period of research. Logistically and financially, arranging Langendorf animal models for further investigation is necessary to build on the preliminary investigations. I had hoped that further study would have allowed us to electrically isolate the left atrial posterior wall via electroporation. As chapter 7 describes, electroporation was attempted in the atrium, but the myocardium was too thin and out equipment to sense and pace the atrial tissue too simplistic. To do this would require three-dimensional mapping equipment that was not available to us.

While different surgical ablation technologies as described in Chapter 1 are available, improving outcomes of ablation at the first stage will be difficult. In Chapter 3, as experience with surgical ablation increased an increasing number of energy deliveries were given to achieve LAPWI. However this did not see an improvement in outcomes following surgical ablation over the study period. It is almost certain that ablation technology will improve but techniques such as electroporation in

chapter 7 offer a “holy grail” of a one-shot energy delivery that results in more durable lesions and complete ablation lines.

To improve outcomes of LAPWI with the current technology described in chapter 2 and 3 I suspect the only option would be more ablation and more rigorous testing resulting in longer procedures. Yet longer procedures and more time spent trying to isolate the LAPW will increase anaesthetic time and complications due to increasing volume of ablation. A technique such as electroporation that is quick and doesn't damage surrounding tissues reduces both these risks.

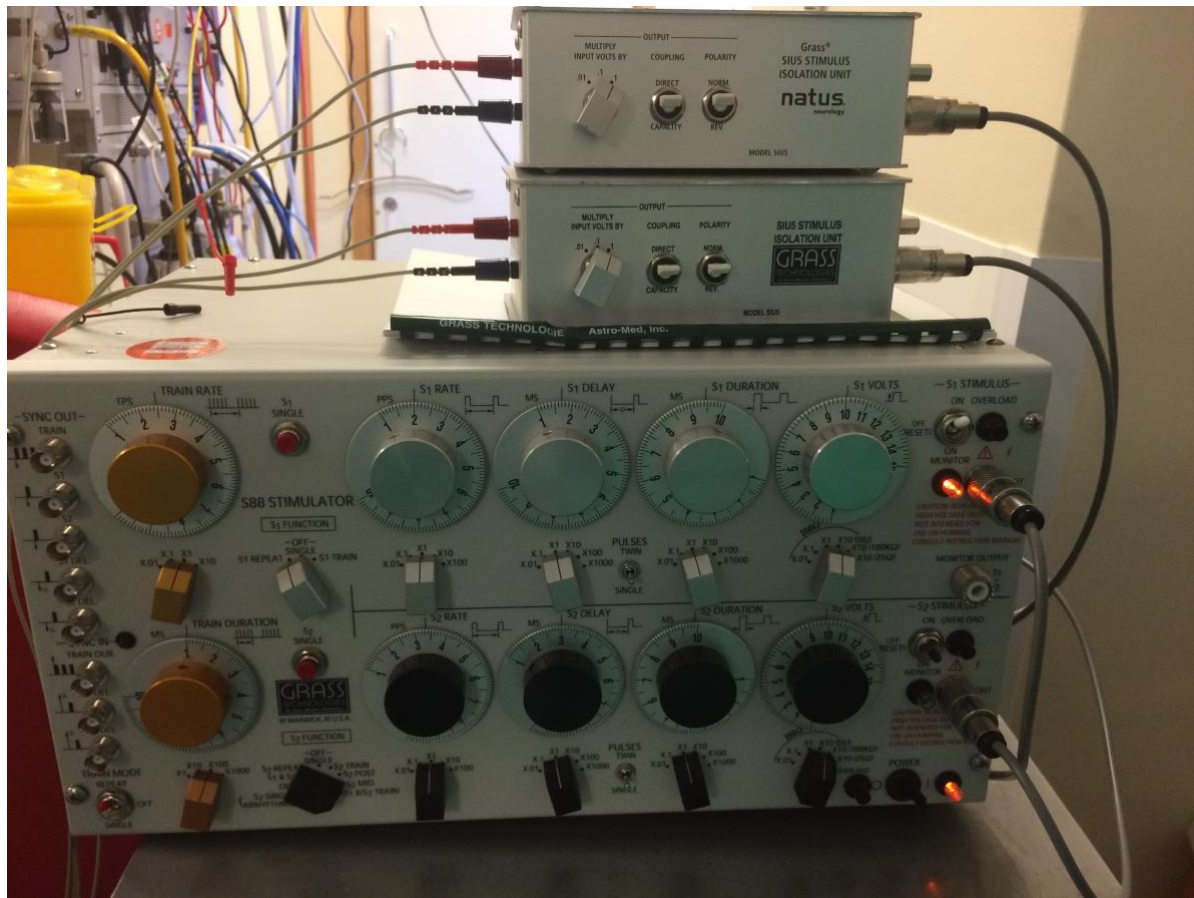
8.3 Differences between catheter and hybrid ablation

As stated above, the groups of patients in Chapters 2 and 3 were not evenly matched and therefore I did not feel it was possible to meaningfully compare outcomes between catheter and hybrid ablation. This was the original idea behind the thesis and so I looked at left atrial posterior wall isolation via two methods through two series and the surrogate marker of P wave duration. Direct comparison is problematic as the hybrid ablation patients had longer continuous AF durations, larger left atria and longer P wave durations at baseline. However, outcomes were similar in both groups despite these negative factors in the hybrid group. Also, a more marked reduction in P wave duration was seen in the hybrid group. I have proposed that this is either due to more enduring lesions in the hybrid ablation group or autonomic modulation from the direct targeting of ganglionic plexi, although it could reflect a more durable and intact lesion with a two-stage procedure.

The two-stage procedure allows for any gaps in the ablation to be identified and re-ablated, meaning better outcomes due to an enduring and more consistent lesion set. However, the targeting of autonomic triggers can improve outcomes of atrial fibrillation ablation and using botulin toxin injected into the GP's following cardiac surgery reduces AF recurrence¹⁵². The location of ganglionic plexi on the posterior left atrium around the pulmonary veins means that they are often ablated with routine pulmonary vein isolation. Freedom from AF may be improved when GP ablation is added to PVI¹⁴⁸ and persistence of ganglionic plexi responses has been associated with worse outcomes following catheter³⁰⁰ and surgical ablation³⁰¹ for AF.

During the study period for this MD I was involved in a study mapping ganglionic plexi at ablation for paroxysmal atrial fibrillation using a GRASS stimulator³⁰². This uses high frequency stimulation to identify ganglionic plexi by inducing a vagal response with bradycardia and occasional hypotension when a GP is stimulated endocardially^{255,303}. Surgical identification of ganglionic plexi works on the same principle with high frequency stimulation on the epicardium identifying ganglionic plexi that can then be excised. This is how the GP's are identified prior to surgical excision in the surgical stage of the hybrid AF ablation pathway described in chapter 3.

Figure 8-1 The GRASS stimulator



Follow-up study of the ablation of ganglionic plexi responses in animal models have demonstrated that reinnervation is common³⁰⁴ and autonomic recovery could impact on outcomes. It has been proposed that epicardial ablation provides more enduring autonomic modulation than endocardial catheter ablation and offers a potential advantage over catheter ablation alone. I therefore designed a study where the ganglionic plexi are mapped before and after left atrial epicardial ablation and GP excision (IRAS 165064). The reduction in GP responses are recorded and re-mapped at catheter second stage to see whether they recur. The hypothesis is that Epicardial ablation eliminates GP responses and that mapping of GP pre and post-surgical epicardial ablation will demonstrate a reduction in GP responses that will persist to the endocardial second stage. In this study it will also be interesting to observe any changes in the surface ECG P wave that correlate with autonomic modulation to test the hypothesis in chapter 4.

The study has started but recruitment had not been sufficient for this work to be included in this thesis.

8.4 Designing a head-to-head trial of catheter and surgical ablation

A future trial comparing hybrid ablation and catheter ablation should focus on symptomatic persistent atrial fibrillation patients and compare a two-stage hybrid ablation with a two-stage catheter ablation approach. It should compare the same lesion pattern, using the Cobra Fusion device in the hybrid group with a second stage catheter ablation to complete left atrial posterior wall isolation. The catheter ablation to isolate the left atrial posterior wall should be as described in chapter 2. Using the series in chapters 2 and 3 as a basis for a future trial due to the limitations explained previously regarding different patient populations with a predominantly long-standing persistent AF population undergoing hybrid ablation with the catheter ablation population having an overall shorter AF duration.

Given the outcomes of the two procedures for persistent AF in our series was 58% freedom from arrhythmia recurrence for catheter ablation at 24 months and 60% in the hybrid group a power calculation can be performed. For 90% power at an alpha value of 0.05 and with 1:1 randomisation 262 patients would be needed. This is a large number to recruit and therefore a non-inferiority study could be appropriate given the expected increased complication rate seen with surgical and hybrid AF ablation.

A study comparing surgical AF ablation using bipolar bilateral ablation clamps and a RF pen with catheter ablation for longstanding persistent atrial fibrillation is currently on-going²²². This is the

first trial of its kind in that it is comparing equivalent lesion patterns, although the catheter group will also receive mitral and tricuspid isthmus lines. Implantable loop recorders will be used as standard so accurate assessment of AF burden will be possible in both groups with symptom scores, complication rates and health economic analysis also reported. As discussed in the introduction, series of surgical and hybrid ablation do appear to show better freedom from atrial fibrillation but this comes at a cost in terms of complications. Comparative studies are therefore essential to allow clinicians and patients to assess the risks and benefits of the two approaches.

8.5 Future uses for oesophageal pacing

The oesophageal pacing technique described in chapter 5 is a potentially valuable tool. Identifying those patients with an intact LAPW lesion pattern and entrance and exit block following a prior ablation could allow earlier discontinuation of anti-arrhythmic drugs and greater confidence of long-term success with rhythm control. For those that do not have demonstrable block via the oesophagus a further ablation or closer follow-up could be recommended.

The technique could be incorporated into trials of hybrid and surgical ablation as a non-invasive marker of posterior wall isolation following the epicardial ablation. In a trial of hybrid versus catheter ablation this could be integrated into the protocol to test for left atrial posterior wall isolation following each stage of the study. If a two-stage procedure is planned then mapping of the left atrium and completion of the 'box' lesion pattern would not be mandated in patients who remained in sinus rhythm at one month follow-up and in whom it was not possible to capture the left atrium from the oesophagus.

Prior to the inclusion of this in any research protocol of a randomised trial comparing catheter and hybrid ablation more studies are required to validate this technique. An outpatient series in patients who have had recurrence of AF after LAPWI is currently on-going at Derriford hospital, Plymouth. The oesophageal study is performed in a pacing lab using fluoroscopy to guide the catheter and sensing and pacing are assessed. If the patient is in persistent atrial fibrillation the procedure is performed following a DC cardioversion. All patients with recurrence of arrhythmia are listed for repeat catheter ablation as standard and we will be able to compare the findings of the oesophageal study with the subsequent catheter study.

It would be interesting to set up a study of surgical AF ablation patients who have undergone LAPWI via a MAZE or thorascopic procedure where an oesophageal study is used at three months to check the lesion set. The hypothesis would be that in those patients where it is possible to capture the left atrium a higher rate of AF recurrence would be seen. Previous work at our centre by Davies et al showed an association between long-term freedom from AF recurrence and ongoing LAPWI in patients who had previously undergone high-frequency focussed ultrasound for AF during concomitant surgery²²⁶. The importance of successful left atrial posterior wall isolation in freedom from atrial fibrillation was also seen in the catheter ablation series in chapter 2. Patients with the complete lesion set had better outcomes than those in whom LAPWI was not possible. These patients could be offered a second catheter ablation to complete the lesion set as standard rather than wait for recurrence. In those in whom successful LAPWI was achieved further intervention could be determined by on-going oesophageal study. Alternatively, asymptomatic patients in whom it is possible to pace from the oesophagus could be more closely followed up. One could hypothesise that there may be more sub-clinical AF in this group of patients that could be detected on ambulatory monitors or implantable loop recorders.

In the first instance it is key to validate the technique with further studies. For oesophageal pacing to be used in a more widespread capacity, proving the benefits of LAPWI in the management of persistent AF will be necessary. Decisions to repeat electrophysiological study and ablation in patients based solely on oesophageal pacing results are not currently justifiable in the absence of symptoms. This thesis would suggest that an intact lesion set and durability of LAPWI is key to outcomes. Consequentially if it can be proven in wider studies that the oesophageal pacing technique can identify patients without an intact lesion set one would expect an increase in arrhythmia recurrence in these patients.

In those patients in whom it is not possible to pace the left atrium from the oesophagus but who have had recurrence of AF the hypothesis of this thesis would point to AF triggers outside the left atrial posterior wall. While this may be a macro-re-entrant atrial flutter, which would be amenable to further ablation, it could point to widespread atrial fibrosis and substrate that would be harder to treat with ablation. In this circumstance the oesophageal study in conjunction with what is known from the previous catheter ablation might point to poorer outcomes from repeat study and acceptance of a rate control strategy. If all the data was available from the mapping procedures in the series in this thesis scar burden inside and outside of the LAPW could be analysed against AF recurrence.

8.6 Future directions for catheter ablation

Outcomes from ablation of persistent atrial fibrillation remain significantly worse than for paroxysmal atrial fibrillation where the well-established lesion set of pulmonary vein isolation is an effective treatment in over 80% of patients. PVI alone has also been shown to provide one year freedom from AF of 59%¹³⁸. It is therefore a reasonable first approach, adopted by many centres, for

patients with persistent AF provided we accept that a significant number will have recurrence.

Currently there is little evidence to justify alternative lesion patterns over PVI but isolating the left atrial posterior wall needs to be considered as either an alternative initial approach or a second line procedure. Improvements in ablation technology that allow for more durable ablation lesions without increase in procedural risks may mean that LAPW isolation via catheter, surgical or hybrid ablation is a first line option for persistent AF in future. At present the more complex procedures are mostly reserved for those with long-standing persistent AF.

New catheter technologies incorporating electroporation potentially offer a quicker procedure with lower risks. The results of Wittkamp's initial animal studies with electroporation is highly promising and suggest a potential role in both epicardial and endocardial ablation^{284–288,305}. If it can be shown that electroporation can give rise to durable ablation lesions, then human study is not far away with alternative catheter technologies utilizing electroporation to ablation either epicardially or endocardially. The modified ALERT catheter allowed for linear ablation. Given that, isolation of the left atrial posterior wall could theoretically be performed with four ablation lines. If technology such as this could reliably isolate the posterior wall of the left atrium with minimal risks to adjacent tissue it could be a valuable tool for the electrophysiologist. Even if the linear ablation was just used for roof or floor lines this is advantageous as it would reduce the risk of damage to the oesophagus, something that is of primary concern to operators ablating on the LAPW.

8.7 Summary

Persistent atrial fibrillation is difficult to treat and its complex pathophysiology, mechanism of onset and propagation are not fully understood. Catheter ablation is better for long-term maintenance of

sinus rhythm than anti-arrhythmic drugs but ablation outside of isolating the pulmonary veins has not been shown to improve outcomes. Much future study is required to answer questions about the best approach for ablation of persistent and long-standing persistent AF. This thesis demonstrates the promise of LAPW isolation and some of its potential advantages over other lesion sets. Randomised comparison is crucial however, both between ways of delivering the lesion pattern and against other patterns such as PVI.

Studies comparing catheter ablation with hybrid and surgical ablation are limited. From series that have been performed previously, and from this thesis, it appears that surgical ablation may have benefits in terms of reduction of arrhythmia but carry a cost in terms of complications. Many of which are major complications. This may ultimately limit surgical techniques and see catheter ablation as the long-term treatment of choice. This is especially true while AF ablation remains a treatment for symptoms without proven prognostic benefits in the majority of patients.

In future studies the technique of oesophageal pacing can be used for follow-up and monitoring of patients. The aim would be to guide the need for repeat procedures which could be offered to those who would potentially gain most. This could both help identify those most at risk of arrhythmia recurrence and reduce the need for unnecessary procedures in those who have intact LAPW lesion sets.

The issues around outcomes from ablation with regard to freedom from arrhythmia and risk of procedural complications may point to the limitations of conventional ablation techniques.

Technological improvements such as electroporation are therefore vital in the advancement of this field. While chapter 7 isn't an obvious fit into this thesis I feel that what I have highlighted in the

introduction is the limitations of ablation in persistent AF and while LAPWI may offer some improvement there is a long way to go. Electroporation is very attractive and human studies will not be too far off. The promise of a safer and better ablation technique in addition to a superior lesion set offers hope to patients in this complex cohort of patients.

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